bluebird bio, Inc.
Form 10-K
February 25, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015

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: 001-35966

bluebird bio, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3680878
(State or Other Jurisdiction of Incorporation or Organization)	(IRS Employer Identification No.)

150 Second Street

Cambridge, Massachusetts	02141
(Address of Principal Executive Offices)	(Zip Code)

(339) 499-9300

(Registrant's Telephone Number, Including Area Code)

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

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

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 x 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 x No ¨

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

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 definitions of "large accelerated filer", "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

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

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

The aggregate market value of common stock held by non-affiliates of the registrant based on the closing price of the registrant's common stock as reported on the Nasdaq Global Select Market on June 30, 2015, the last business day of the registrant's most recently completed second quarter, was $6,054,326,404.

As of February 18, 2016, there were 36,927,638 shares of the registrant's common stock, par value $0.01 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement relating to its 2016 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "seek," "s "would," or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the initiation, timing, progress and results of our preclinical and clinical studies, and our research and development programs;
- our ability to advance product candidates into, and successfully complete, clinical studies;
- our ability to advance our viral vector and drug product manufacturing capabilities;
- the timing or likelihood of regulatory filings and approvals;
- the timing or success of commercialization of our product candidates, if approved;
- the pricing and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations and licenses;
- developments relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

PART I

Item 1. Business

Overview

We are a clinical-stage biotechnology company committed to developing potentially transformative gene therapies for severe genetic and rare diseases and in the field of T cell-based immunotherapy. With our lentiviral-based gene therapies, T cell immunotherapy expertise and gene editing capabilities, we have built an integrated product platform with broad potential application in severe genetic and rare diseases and in oncology. We believe that gene therapy has the potential to change the way these patients are treated by correcting the underlying genetic defect that is the cause of their disease, rather than offering treatments that only address their symptoms. Our gene therapy clinical programs include our LentiGlobin® product candidate to treat transfusion-dependent -thalassemia, or TDT, which we previously referred to as -thalassemia major, and severe sickle cell disease, or severe SCD, and our Lenti-D™ product candidate to treat cerebral adrenoleukodystrophy, or CALD, a rare hereditary neurological disorder that we previously referred to as childhood cerebral adrenoleukodystrophy, as patients affected with this disorder are often young boys. Our oncology programs are built upon our leadership in lentiviral gene delivery and T cell engineering, with a focus on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies. Our lead oncology program, bb2121, is a CAR T cell product candidate targeting B-cell maturation antigen, or BCMA, in multiple myeloma. We also have discovery research programs utilizing megaTALs/homing endonuclease gene editing technologies with the potential for use across our pipeline.

We are conducting three clinical studies of our LentiGlobin product candidate in a variety of rare, hereditary blood disorders that often lead to severe anemia and shortened lifespans: a global Phase I/II study, called the Northstar Study, for the treatment of TDT; a single-center Phase I/II study in France (HGB-205) for the treatment of TDT and severe SCD; and a Phase I study in the United States (HGB-206) for the treatment of severe SCD. Our LentiGlobin product candidate has been granted Orphan Drug status by the U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, for the treatment of both -thalassemia and SCD. Our LentiGlobin product candidate was granted Fast-Track designation by the FDA for the treatment of -thalassemia major in January 2013 and for the treatment of certain patients with severe SCD in May 2014. In January 2015, the FDA granted Breakthrough Therapy designation to our LentiGlobin product candidate for the treatment of transfusion-dependent patients with -thalassemia major.

We are conducting a Phase II/III clinical study, called the Starbeam Study, of our Lenti-D product candidate, to evaluate its safety and efficacy in pediatric and adolescent subjects with CALD. We are also conducting an observational study of subjects with CALD treated by allogeneic hematopoietic stem-cell transplant (ALD-103). Our Lenti-D product candidate has been granted Orphan Drug status by the FDA and the EMA for the treatment of adrenoleukodystrophy.

In February 2016, we initiated a Phase I clinical study in the United States (CRB-401) of our bb2121 product candidate for the treatment of relapsed/refractory multiple myeloma. bb2121 is the lead CAR T cell-based immunotherapy product candidate from our collaboration with Celgene Corporation, or Celgene. The collaboration has focused on applying gene therapy technology to genetically modify a patient's own T cells to target and destroy cancer cells. T cells modified to express a CAR have been shown by academic and corporate researchers to have beneficial effects in human clinical trials for patients with a variety of lymphomas. We have licensed to Celgene the right to develop and commercialize our bb2121 product candidate following the completion of the ongoing Phase I clinical study, and we may exercise our option to co-develop and co-promote this product candidate.

In June 2014, we acquired Precision Genome Engineering, Inc., or Pregenen, a privately-held biotechnology company headquartered in Seattle, Washington. Through the acquisition, we obtained rights to Pregenen's gene editing technology platform and cell signaling technology, and have integrated these technologies and research team and expanded our related discovery research efforts. We are focused on utilizing homing endonuclease and megaTAL gene editing technologies in a variety of potential applications and disease areas, including for oncology and hematology. Homing endonucleases and MegaTALs are novel enzymes that provide a highly specific and efficient way to modify DNA sequences to silence, edit or insert genetic components to potentially treat a variety of diseases.

Our gene therapy platform is based on viral vectors that utilize a modified, non-replicating version of the Human Immunodeficiency Virus Type 1, or HIV-1, that has been stripped of all of the components required for it to self-replicate and infect additional cells. HIV-1 is part of the lentivirus family of viruses, and we refer to our vectors as lentiviral vectors. Our lentiviral vectors are used to introduce a functional copy of a gene to the patient's own isolated blood stem cells, called hematopoietic stem cells, or HSCs, which reside in a patient's bone marrow and are capable of differentiating into a wide range of cell types. HSCs are dividing cells, thus our approach allows for sustained expression of the modified gene as we are able to take advantage of a lifetime of replication of the gene-modified HSCs. Additionally, we have developed a proprietary cell-based vector manufacturing process that is both reproducible and scalable. We believe our innovations in viral vector design and related manufacturing processes are important steps towards advancing the field of gene therapy and in realizing its full potential on a commercial scale.

Utilizing our gene therapy platform, we are developing product candidates comprising the patient's own gene-modified HSCs. Clinical proof-of-concept already exists for allogeneic hematopoietic stem cell transplant, or HSCT, an approach of treating a patient with HSCs contributed by a donor other than the patient that contain the properly functioning copy of the gene whose mutation has caused the underlying disease. However, this approach has significant limitations, including difficulties in finding appropriate genetically-matched donors and the risk of transplant-related rejection, graft-versus-host disease, or GVHD, and mortality, and is therefore typically only available on a limited basis. Our approach is intended to address the significant limitations of allogeneic HSCT while utilizing existing stem cell transplant infrastructure and processes. Also, because our approach has the potential to drive sustained expression of the functional protein encoded by the gene insert after potentially a single-administration, we believe the value proposition offered by our product candidates for patients, families, health care providers and payors would be significant.

Although our initial focus for HSCs is in TDT, severe SCD and CALD, and for T cells is in oncology, we believe our gene therapy platform has broad therapeutic potential in a variety of indications. We believe that our vectors can be used to introduce virtually any gene into a cell and have the potential to be manufactured on a commercial scale reproducibly and reliably, as each new vector is produced using substantially the same process. We also take advantage of lentivirus' ability to transduce HSCs more efficiently than other vectors, such as those derived from another virus used in gene therapy approaches, called adeno-associated virus, or AAV, which gives us the potential to address diseases in a variety of cell lineages beyond those that are derived from HSCs, such as microglia (useful for CALD), red blood cells (useful for ß-thalassemia and SCD), T cells (useful for cancer and immunology) and others.

Our gene therapy platform and proprietary lentiviral vectors

Our gene therapy product candidates for severe genetic and rare diseases and in oncology are being developed based on a simple notion: to genetically modify a patient's own cells to fundamentally correct or address the genetic basis underlying a disease. Although the notion of gene transfer to a patient's own cells is simple, the processes of developing viral vectors capable of delivering the genetic material and inserting gene sequences safely into a patient's target cells is highly technical and demands significant expertise, experience and know-how. Leveraging our extensive expertise in viral vector design and manufacturing and transduction, we have developed a gene therapy platform that we believe is broadly applicable in a variety of indications with significant unmet medical need.

The success of a gene therapy platform is highly dependent on the type of delivery system used. Our platform is based upon an ex vivo viral delivery system whereby a certain type of virus delivers the DNA that it is carrying into a cell and inserts this DNA into the cell's genome. We have developed significant expertise in designing a particular type of vector delivery system employing a lentivirus for use in gene therapy and have also developed and in-licensed relevant intellectual property, including know-how, related to lentiviral vectors. Our lentiviral construct design includes only the minimal viral components of HIV-1 required to enable the vector to undergo one round of replication within the cell during manufacturing and subsequently to enter the target cells and deliver the gene that it is carrying.

We believe that our lentiviral vectors are particularly well-suited for treating a number of diseases and have certain advantages over other viral vectors used in developing gene therapy products, including:

- Sustained expression—Unlike other vectors based on viruses such as AAV, lentiviral vectors are capable of integrating the functional gene they carry into the DNA of the target cell's genome. As such, they are well-suited to introduce a sustained therapeutic effect in dividing cells because the gene sequence introduced by the lentiviral vector will be replicated with the rest of the cell's chromosomal DNA and subsequent dividing cells will also carry the newly inserted gene sequence. Other vector platforms that take advantage of different viruses introduce genes into cells but they don't actively integrate into a cell's DNA and require many viral events to transform a cell.
- Potentially Improved Safety—In clinical studies of gene therapy product candidates conducted by other entities, earlier generations of integrating viral vectors based on a mouse gamma-retrovirus were shown to preferentially integrate

into certain regulatory regions of genes (such as the promoter regions) and in some instances inappropriately activate the cell to divide uncontrollably, leading to cancer through a process called insertional oncogenesis. These genetic alterations have led to several well-publicized adverse events, including several reported cases of leukemia, and highlighted the need to develop new gene therapy vectors with potentially improved safety profiles. Next generation lentiviral vectors, unlike gamma retroviruses, have a distinct pattern of integrating into regions that provide instructions for making proteins rather than preferentially integrating into regions that can lead to cell proliferation and cancer. We believe this difference in integration patterns is a critical factor in potentially improving the safety profile of the vector, and distinguishes them from earlier generations of integrating viral vectors.

- Carrying capacity—Unlike AAV, the lentivirus is able to carry large therapeutic gene sequences (up to 8,000 base pairs) into a host cell. This may limit the utility of AAV in some diseases where the required gene sequences will be too large to fit into an AAV construct. In this regard, lentiviral vectors offer more flexibility.

Hematopoietic Stem Cells (HSCs)

Our gene therapy platform takes advantage of lentiviral vectors' ability to stably integrate into the target cell's genome by focusing on diseases we can treat through genetic modification of HSCs, which when reintroduced back into the patient, differentiate into numerous other cell lineages, as depicted below. We believe our initial clinical indications—CALD, TDT and severe SCD—can all be treated by introducing a specific functional gene into HSCs taken from the patient to correct the gene defect responsible for the disease.

HSCs are dividing stem cells that are permanently found in a patient's bone marrow and are an ongoing replacement source of mature cell types as they die off. HSCs produce progeny cells, called progenitors, that differentiate into all of the cellular elements that compose the blood, including red blood cells (useful for ß-thalassemia and SCD), microglia (useful for CALD), T cells (useful for cancer and immunology) and others. As such, all progenitors derived from a single gene therapy-modified HSC will carry the same corrective genetic modification, which we believe gives our approach the potential to deliver life-long clinical benefits based on a single therapeutic administration.

Our therapeutic approach in HSCs

The delivery of a gene therapy product in HSCs requires several steps. Importantly, our approach seeks to leverage cell transplant procedures and infrastructure already widely used in the clinic for allogeneic HSCT.

1. We produce our lentiviral vector by co-transfecting a packaging cell line with multiple plasmids that separately encode the various components of the virus as well as the functional gene sequence the viral vector will carry. The use of multiple plasmids is an important safety step designed to further prevent the resulting lentiviral vectors from being able to replicate and cause infection on their own.
2. For the treatment of severe genetic and rare diseases, a sample of the patient's own HSCs is extracted and isolated through a standard process known as apheresis, where HSCs are first mobilized into the blood stream from the bone marrow using a routinely-used pharmaceutical agent and then collected from the patient's blood. In some cases, such as for the treatment of severe SCD, HSCs are extracted directly from the patient's bone marrow.
3. The lentiviral vector is mixed with the patient's isolated HSCs ex vivo. This leads to the insertion of the functional gene into the HSCs' existing DNA, thus creating a pool of the patient's own, or autologous, gene-modified cells. The cells are then washed to remove any remnants of the viral vector or culture media. These gene-modified cells are the therapeutic drug product that is delivered back into the patient.
4. Prior to administering our drug product, the patient undergoes a standard myeloablation procedure (also used in allogeneic HSCT) to remove endogenous bone marrow cells. The modified HSCs are then re-infused back into the patient (approximately one to two months after initial extraction of the patient's HSCs) and begin re-populating a portion of the bone marrow as permanently modified HSCs in a process known as engraftment. The engrafted HSCs will go on to give rise to progenitor cell types with the functional gene.

Our therapeutic approach in T cell-based immunotherapy

Similarly to our therapeutic approach in HSCs, the delivery of modified T cell products requires several steps. Importantly, our approach seeks to leverage cell transplant procedures and infrastructure already widely used in the clinic for allogeneic bone marrow transplant.

1. We produce our lentiviral vector by co-transfecting a packaging cell line with multiple plasmids that separately encode the various components of the virus as well as the tumor-targeting protein the viral vector will carry.
2. For the treatment of cancer, a sample of the patient's own white blood cells is extracted and isolated through a standard process known as leukapheresis, in which white blood cells are separated from the remaining fractions of the patient's blood.
3. The lentiviral vector is mixed with the patient's white blood cells, which include T cells, ex vivo. This leads to the insertion of the gene encoding a CAR into the T cells' existing DNA, thus creating a population of modified T cells expressing a CAR or TCR. The cells are then washed to remove any remnants of the viral vector or culture media and expanded to increase the number of modified T cells to the required dosage. These modified T cells are the therapeutic drug product that is delivered back into the patient.
4. Prior to administering our drug product, the patient undergoes a standard lymphodepletion procedure to reduce the number of T cells that may compete with the modified T cells. The modified T cells are then re-infused back into the patient.

Our product candidate pipeline

We are developing our LentiGlobin product candidate to treat patients with TDT and severe SCD. We are conducting two Phase I/II clinical studies in the United States, Australia, and Thailand and in France, called the Northstar and HGB-205 studies, respectively, of our LentiGlobin product candidate to evaluate its safety and efficacy in subjects with TDT and severe SCD. We have initiated a Phase I clinical study in the United States, called the HGB-206 study, to evaluate the safety and efficacy of our LentiGlobin product candidate in subjects with severe SCD. We are developing our Lenti-D product candidate to treat patients with CALD, the most severe form of ALD. We are also currently conducting a Phase II/III clinical study of our Lenti-D product candidate in the United States, which we refer to as the Starbeam Study, to examine the safety and efficacy of our Lenti-D product candidate in preserving neurological function and stabilizing cerebral demyelination in subjects with CALD.

We are also pursuing opportunities to apply our gene therapy platform technologies in the field of immunotherapy in oncology by genetically modifying a patient's own T cells to target and destroy cancer cells. Our collaboration with Celgene focuses on CAR T cell therapy, which has been shown by academic and corporate researchers to have beneficial effects in clinical trials for patients with a variety of lymphomas. Our collaboration with Celgene is focused on product candidates directed against BCMA, a protein expressed on the surface of multiple myeloma cells and plasma cells. In February 2016, we initiated a Phase I clinical study (CRB-401) to evaluate the safety and effectiveness of our bb2121 product candidate, the lead product candidate from this collaboration, in the treatment of relapsed/refractory multiple myeloma. Celgene has exercised its option to exclusively license our bb2121 product candidate, while we have retained an option to co-develop and co-promote this product candidate. We are also collaborating with Kite Pharma, Inc. in the development of a second-generation T cell receptor, or TCR, T cell therapy against HPV-16 E6 antigen, which is related to certain cancers associated with the human papilloma virus.

Our LentiGlobin product candidate opportunity

ß-thalassemia

Overview

ß-thalassemia is a rare hereditary blood disorder caused by a genetic abnormality of the ß-globin gene resulting in defective red blood cells, or RBCs. Genetic mutations cause the absence or reduced production of the beta chains of

hemoglobin, or ß-globin, thereby preventing the proper formation of hemoglobin A, which normally accounts for greater than 95% of the hemoglobin in the blood of adults. Hemoglobin is an iron-containing protein in the blood that carries oxygen from the respiratory organs to the rest of the body. Hemoglobin A consists of four chains—two chains each of a-globin and ß-globin. Normally existing at an approximate 1:1 ratio, genetic mutations that impair the production of ß-globin can lead to a relative excess of a-globin, leading to premature death of red blood cells. The clinical implications of the a-globin/ß-globin imbalance are two-fold: first, patients lack sufficient RBCs and hemoglobin to effectively transport oxygen throughout the body and can become severely anemic; and second, the shortened life span and ineffective production of RBCs can lead to other complications such as splenomegaly, marrow expansion, bone deformities, and iron overload in major organs.

The clinical course of ß-thalassemia correlates with the degree of globin chain imbalance. Nearly 200 different mutations have been described in patients with ß-thalassemia. The clinical presentation varies widely, dependent largely upon the type of inherited mutation. Mutations can be categorized as those which result in no functional ß-globin production ($ß^{0}$) and those which result in decreased functional ß-globin production ($ß^{+}$). TDT refers to any mutation pairing that results in the need for chronic transfusions due

to severe anemia, and is the clinical finding in most patients with ß°/ß° genotype as well as many patients with other genotypes resulting in abnormal ß-globin production, such as the ß°/ß$^{+}$ and ß$^{+}$/ß$^{+}$ genotypes. Affected patients produce as little as one to seven g/dL of hemoglobin (while a normal adult produces 12-18 g/dL of hemoglobin). Hemoglobin E (ß^{E}), which is another ß-globin mutation and is usually asymptomatic, can also result in TDT when paired with the ß° or ß$^{+}$ mutations.

ß-thalassemia is concentrated in populations of Mediterranean, South and Southeast Asian and Middle Eastern descent. It has been estimated that about 1.5% (80 to 90 million people) of the global population are carriers of ß-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world, while the condition is considered rare in the United States and Europe. According to Thalassemia International Federation, about 288,000 patients with TDT are alive and registered as receiving regular treatment around the world, of which it is estimated that about 15,000 live in the United States and Europe. Due to the rarity of this disease in the United States, published research on the prevalence of ß-thalassemia in the United States is limited.

Limitations of current treatment options

In geographies where treatment is available, patients with TDT receive chronic blood transfusion regimens. These regimens consist of infusions with units of packed RBC, or pRBC, every three to five weeks, the timing of which is aimed at maintaining hemoglobin levels and controlling symptoms of the disease. While chronic blood transfusions can be effective at minimizing the symptoms of TDT, they often lead to iron overload, which over time leads to mortality through iron-associated heart and liver toxicity. To prevent iron overload-associated risks, patients must adhere to therapeutic iron chelation regimens to reduce the iron overload. Poor compliance with chelation regimens remains a key challenge; it is estimated that with typical compliance, the overall life expectancy for a patient with TDT is significantly reduced compared to the general population. Even patients who are compliant with transfusion and iron chelation regimens can experience a reduced quality of life due to the burden and side effects of therapy and the fluctuating levels of hemoglobin on a month-to-month basis.

The only potentially curative therapy for ß-thalassemia today is allogeneic HSCT. However, complications of allogeneic HSCT include a 10-30% risk of engraftment failure in Human-Leukocyte-Antigen, or HLA, matched patients, a 12-16% incidence of life-threatening infection, and an approximately 30% risk of GVHD, a common complication in which donor immune cells (white blood cells in the graft) recognize the cells of the recipient (the host) as “foreign” and attack them. As a result of these safety challenges, allogeneic HSCT can lead to significant mortality rates, particularly for patients treated with cells from a donor who is not a matched sibling, and in older patients. Consequently, transplants are offered primarily to pediatric patients with a matched sibling donor, which occurs in less than 25% of all cases. In addition, because of the need for immunosuppression following allogeneic HSCT, there is a risk of opportunistic infections and other serious side effects associated with immunosuppressive drugs. Overall, TDT remains a devastating disease with an unmet medical need.

In many developing countries where ß-thalassemia is more prevalent, such as Thailand, the lack of readily available chronic blood transfusions and optimal iron chelation regimens represents a significant societal challenge. In these countries, children with TDT have a poor prognosis and experience growth retardation, hepatosplenomegaly, or enlargement of the spleen, and skeletal deformities resulting from extra-medullary hematopoiesis. Ultimately, premature death is not uncommon. We believe that alternative therapies, such as those represented by our gene therapy approach, could offer a potential solution to the challenges of treating ß-thalassemia patients across the world.

Sickle cell disease

Overview

Sickle cell disease, or SCD, is a hereditary blood disorder resulting from a mutation in the ß-globin gene that causes polymerization of hemoglobin proteins and abnormal red blood cell function. The disease is characterized by anemia,

vaso-occlusive pain crisis (a common complication of SCD in which there is severe pain due to obstructed blood flow in the bones, joints, lungs, liver, spleen, kidney, eye, or central nervous system), infections, stroke, overall poor quality of life and early death in a large subset of patients. Under low-oxygen conditions, which are exacerbated by the RBC abnormalities, the mutant hemoglobin aggregates causing the RBCs to take on a sickle shape (sickle cells), which causes them to aggregate and obstruct small blood vessels, thereby restricting blood flow to organs resulting in pain, cell death and organ damage. If oxygen levels are restored, the hemoglobin can disaggregate and the RBCs will return to their normal shape, but over time, the sickling damages the cell membrane and the cells fail to return to the normal shape even in high-oxygen conditions. Additionally, the sickle-shaped RBCs tend to rupture more easily, often resulting in damage to the blood vessels and iron overload that can ultimately lead to organ failure and death.

SCD is concentrated in populations of African, Middle Eastern and South Asian descent. The global incidence of SCD is estimated to be 250,000-300,000 births annually, and the global prevalence of the disease is estimated to be about 20-25 million. In the United States, where SCD is a standard part of many states' newborn screening procedures, the incidence is more than 1,600 births annually with an estimated prevalence of 100,000 individuals.

Limitations of current treatment options

Where adequate medical care is available, common treatments for patients with SCD largely revolve around management and prevention of acute sickling episodes. Chronic management may include hydroxyurea and, in certain cases, chronic transfusions. Hydroxyurea is currently the only medication approved for the treatment of severe SCD and is recommended for patients with recurrent episodes of acute pain or specific frequencies of painful crises or life-threatening complications. Not all severe SCD patients respond to hydroxyurea however, or are able to tolerate the cytotoxic effect of reduced white blood cell and platelet counts. Thus, a significant number of patients with SCD find it difficult to adhere to hydroxyurea treatment, and for most patients there is no effective long-term treatment.

RBC transfusion therapy can be utilized to maintain the level of sickling hemoglobin below 30%, which decreases sickling of RBCs, increases their oxygen-carrying capacity, reduces the risk of recurrent stroke, and decreases the incidence of associated co-morbidities. While standard blood transfusions are often used to achieve this goal, especially during acute episodes, exchange transfusions offer better control of blood volume and viscosity while decreasing the risk of transfusion-related haemochromatosis and iron overload in the chronic setting. While transfusion therapy can be critical in the management of acute disease, and can be vital in preventing some of the chronic manifestations of severe SCD, it does not provide equal benefit to all patients.

Similar to TDT, the only potentially curative therapy currently available for SCD is allogeneic HSCT, however because of the significant risk of transplant-related morbidity and mortality, this option is usually offered primarily to pediatric patients with available sibling-matched donors. It is particularly difficult to find suitable donors for individuals of African descent, and it is estimated that approximately 10% of eligible patients do so. In light of these factors, we believe SCD is a devastating disease with a significant unmet medical need.

Our LentiGlobin product candidate

We are developing our LentiGlobin product candidate as a potential one-time treatment for both TDT and severe SCD. Our approach involves the ex vivo insertion of a single codon variant of the normal ß-globin gene using a lentiviral vector into the patient's own HSCs to enable formation of normally functioning hemoglobin A and normal RBCs in patients. Importantly, this codon variant, referred to as T87Q, also serves as a distinct biomarker used to quantify expression levels of the functional ß-globin protein in patients with TDT and severe SCD, while also providing anti-sickling properties in the context of SCD. We refer to the HSCs that have undergone gene modification ex vivo as the final LentiGlobin drug product, or our LentiGlobin product candidate.

We are conducting two Phase I/II clinical studies of our LentiGlobin product candidate, to evaluate its safety and efficacy in subjects with TDT. In December 2013, we announced that the first subject with TDT had been treated in our French study of our LentiGlobin product candidate, called the HGB-205 study, which also permits the enrollment of subjects with severe SCD. In October 2014, we announced that the first subject with severe SCD had been treated in the HGB-205 study. In March 2014, we announced that the first subject with TDT had been treated in our other study of our LentiGlobin product candidate being conducted in the United States, Australia and Thailand, called the Northstar Study. We presented interim results from both the HGB-205 study and the Northstar Study at the American Society of Hematology Annual Meeting in December 2015.

We have initiated a Phase I clinical study in the United States, called the HGB-206 Study, to evaluate the safety and efficacy of our LentiGlobin product candidate in subjects with severe SCD. Additionally, we are in discussions with the FDA regarding our planned Phase III clinical studies for the treatment of TDT in subjects who do not have the ß°/ß° genotype. We believe that data from these studies, together with data from the ongoing Northstar and HGB-205 studies could form the basis for a biologics licensing application, or BLA, submission for our LentiGlobin product candidate in the United States. These planned clinical studies could support an accelerated approval, with post-approval confirmatory evidence to be provided with longer-term follow-up of these studies.

Our LentiGlobin product candidate has been granted Orphan Drug status by the FDA and EMA for both -thalassemia and SCD. Our LentiGlobin product candidate was granted Fast-Track designation by the FDA for the treatment of -thalassemia major in January 2013 and for the treatment of certain patients with severe SCD in May 2014. In January 2015, the FDA granted Breakthrough Therapy designation to our LentiGlobin product candidate for the treatment of transfusion-dependent patients with -thalassemia major. We are participating in the EMA's Adaptive Pathways pilot program (formerly referred to as Adaptive Licensing), which is part of the EMA's effort to improve timely access for patients to new medicines. Based on our discussions involving the EMA, European Health Technology Assessment agencies and patient advocacy organizations as part of this program, we believe it is possible to seek conditional approval for the treatment of adults and adolescents with TDT on the basis of the totality of the clinical data, in particular reduction in transfusion need, from the ongoing Northstar study and supportive HGB-205 study, assuming these studies demonstrate acceptable efficacy and safety. We believe that conversion to full approval would be subject to the successful completion of our planned Phase III clinical studies, supportive long-term follow-up data and "real-life" post-approval monitoring data. Whether or not our clinical data are sufficient to support conditional, and ultimately full, approval will be a review decision by the EMA.

Clinical development of our LentiGlobin product candidate

The HGB-205 Phase I/II clinical study for TDT and severe SCD

The HGB-205 study is a Phase I/II clinical study to examine the safety and efficacy of our LentiGlobin product candidate in up to seven subjects with a diagnosis of TDT or severe SCD. Study subjects must be between five and 35 years of age with a diagnosis of TDT or severe SCD. In December 2013, we announced that the first subject with TDT had been treated in the HGB-205 study and in October 2014 we announced that the first subject with severe SCD had been treated in the European HGB-205 study. To be enrolled, subjects with TDT must have received at least 100 mL/kg/year of pRBCs per year for the past two years. Those with severe SCD must have failed to achieve clinical benefit from treatment with hydroxyurea and have an additional poor prognostic risk factor (e.g., recurrent vaso-occlusive crises or acute chest syndromes). All subjects must be eligible for allogeneic HSCT, but without a matched sibling allogeneic HSCT donor.

For all subjects, efficacy will be measured by RBC transfusion requirements per month and per year, post-transplant and the number of total in-patient hospitalization days (post-transplant discharge) at six, 12 and 24 months. For severe SCD patients only, efficacy will be measured by the number of vaso-occlusive crises or acute chest syndrome events at six, 12 and 24 months and evaluation of changes in the nature or frequency of the subject-specific main inclusion criteria.

Safety evaluations to be performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any subject and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia.

Interim Clinical Data from the HGB-205 Study

In December 2015, we presented interim clinical data from the HGB-205 study at the Annual Meeting of the American Society of Hematology, or ASH. As of the data cut-off date of November 10, 2015, four subjects with TDT and one subject with severe SCD had undergone infusion with LentiGlobin drug product in the HGB-205 study. The two subjects with TDT for which we have at least 12 months of follow up data achieved rapid transfusion independence with near-normal hemoglobin levels and are producing steadily increasing amounts of $ß^{A\text{-}T87Q}$-globin, similar to what may be expected from a successful allogeneic transplant. As of November 10, 2015, these two subjects had been free from the need for transfusions for 23.4 months and 20.1 months, respectively. An additional two patients with TDT had been infused, although it was too early to draw any meaningful efficacy conclusions. At their most recent follow ups, three months and one month, respectively, these patients were producing measurable levels of $ß\text{-}^{T87Q}$-globin. At the twelve-month post-infusion follow up for the subject with severe SCD, the proportion of anti-sickling hemoglobin accounted for 49 percent of all hemoglobin production, which is above the 30 percent threshold expected to potentially achieve a disease-modifying clinical effect. Prior to infusion, this subject required chronic blood transfusions. Since infusion with LentiGlobin drug product, this subject was successfully weaned off of transfusions and has remained transfusion free for more than nine months. Since infusion, this subject has had no hospitalizations or acute SCD-related events. In this study, treatment with our LentiGlobin product candidate has been well tolerated, with no drug product-related adverse events observed as of November 10, 2015. Below is a table summarizing the interim clinical data from the HGB-205 study presented at the ASH annual meeting in December 2015:

	TDT	Severe SCD

Patient	1201	1202	1203	1206	1204
Enrollment age	18	16	19	17	13
Genotype	0/ E	0/ E	homozygous IVS1 nt 110 G>A	0/ E	S/ S
Transfusion requirements prior to study entry (mls/kg/year)	139	188	176	197	170
CD34+ VCN	1.5	2.1	0.8	1.1	1.2/1.0*
CD34+ cell count	8.9	13.6	8.8	12.0	5.6
($x10^6$/kg)					
Days to neutrophil engraftment	Day +13	Day +15	Day +28	Day +16	Day +37
HbA^{T87Q}/total Hb (g/dL)	7.9/10.8	10.3/13.1	4.3/8.0	2.1/10.6	5.5/11.7
Last study follow up visit (months)**	21	18	4.5	1	12

*VCN is an abbreviation for Vector Copy Number, which is a measurement of the mean number of viral vectors in a population of cells, in this case, of the LentiGlobin drug product prior to infusion of the study subject. If more than one drug product was manufactured for a subject, the VCN of each drug product lot is quantified and the cell count is combined.

**Last scheduled study visit for which results were available as of November 10, 2015.

It should be noted that these data presented above are current as of the dates presented, are preliminary in nature and the HGB-205 study is not complete. There is limited data concerning long-term safety and efficacy following treatment with our LentiGlobin

product candidate. These data may not continue for these subjects or be repeated or observed in ongoing or future studies involving our LentiGlobin product candidate, including the HGB-205 study, the Northstar Study or the HGB-206 study. It is possible that subjects for whom transfusion support has been reduced or eliminated may receive transfusion support in the future.

The Northstar Phase I/II clinical study for TDT

The Northstar Study is a single-dose, open-label, non-randomized, multi-site Phase I/II clinical study in the United States, Australia and Thailand to evaluate the safety and efficacy of the LentiGlobin product candidate in increasing hemoglobin production and eliminating or reducing transfusion dependence following treatment. In March 2014, we announced that the first subject with TDT had been treated in our Northstar Study.

Up to 18 adults and adolescents will be enrolled in the study. Study subjects must be between 12 and 35 years of age with a diagnosis of TDT and receive at least 100 mL/kg/year of pRBCs or greater than or equal to eight transfusions of pRBCs per year in each of the two years preceding enrollment. The subjects must also be eligible for allogeneic HSCT.

Efficacy will be evaluated primarily by the production of ³2.0 g/dL of hemoglobin A containing $ß^{A-T87Q}$-globin for the six-month period between 18 and 24 months post-transplant. In order to allow for endogenous hemoglobin production following transplant, subjects will be transfused with RBCs only when total hemoglobin decreases below 7.0 g/dL. The rationale for this endpoint is that production of ³2.0 g/dL of hemoglobin A containing $ß^{A-T87Q}$-globin represents a clinically meaningful increase in endogenous hemoglobin production that would be expected to diminish transfusion requirements, and could result in transfusion independence in TDT subjects.

Exploratory efficacy endpoints include RBC transfusion requirements (measured in milliliters per kilogram) per month and per year, post-transplant. Safety evaluations to be performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any subject and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Subjects will be monitored by regular screening. Each subject will remain on study for approximately 26 months from time of consent and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond 24 months.

Interim Clinical Data from the Northstar Study

In December 2015, we presented interim clinical data from the Northstar Study at the ASH Annual Meeting. As of the data cut-off date of October 28, 2015, 13 subjects with TDT had undergone infusion with LentiGlobin drug product in the Northstar Study. As of October 28, 2015, nine of these subjects had at least six months follow up following infusion. The median $ß^{A-T87Q}$ production range for these nine subjects was 4.9 g/dL, and was 4.9 g/dL among the five subjects with the non-$^0/^0$ genotypes, and was 5.0 g/dL among the four subjects with the $^0/^0$ genotype. The five subjects with non-$^0/^0$ genotypes with at least six months follow up have been free from the need for transfusions, ranging from 7.1 to 16.4 months of ongoing transfusion independence. The four subjects with the $^0/^0$ genotype experienced a reduction in transfusion volume from 33 percent to 100 percent. In the Northstar Study, treatment with our LentiGlobin product candidate has been consistent with autologous transplantation, with no drug product-related Grade 3 or greater adverse events observed as of October 28, 2015.

It should be noted that these data presented above are current as of the dates presented, are preliminary in nature and the Northstar Study is not complete. There is limited data concerning long-term safety and efficacy following treatment with our LentiGlobin product candidate. These data may not continue for these subjects or be repeated or observed in ongoing or future studies involving our LentiGlobin product candidate, including the HGB-205 study, the Northstar Study or the HGB-206 study. It is possible that subjects for whom transfusion support has been reduced or eliminated may receive transfusion support in the future.

The HGB-206 clinical study for severe sickle cell disease

The HGB-206 Study is a single-dose, open-label, non-randomized, multi-site Phase I clinical study in the United States to evaluate the safety and efficacy of the LentiGlobin product candidate to treat severe SCD.

Up to 20 adults will be enrolled in the study. Study subjects must be ≥18 years of age with a diagnosis of sickle cell disease, with either $^{S/S}$ or $^{S/0}$ genotype. The sickle cell disease must be severe, as defined by recurrent severe vaso-occlusive events, acute chest syndrome, history of an overt stroke, or echocardiographic evidence of an elevated tricuspid regurgitation jet velocity, an indicator of pulmonary hypertension, and subjects must have failed to achieve clinical benefit from treatment with hydroxyurea. The subjects must also be eligible for HSCT.

Efficacy endpoints include changes in the frequency of severe vaso-occlusive crises, acute chest syndrome, and strokes or ischemic attacks. Pharmacodynamic endpoints include measurements of transgene persistence and transgene expression.

Safety endpoints include monitoring for laboratory parameters and frequency and severity of adverse events; the success and kinetics of HSC engraftment; the incidence of treatment related mortality and overall survival; the detection of vector-derived replication-competent lentivirus in any subject; and the characterization of events of insertional mutagenesis leading to clonal dominance or leukemia.

Each subject will remain on study for approximately 26 months from time of consent and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond 24 months.

Preliminary Clinical Data from the HGB-206 Study

In December 2015, we presented preliminary clinical data from the HGB-206 study at the ASH Annual Meeting. As of the data cut-off date of November 17, 2015, LentiGlobin drug product had been manufactured for four patients with severe SCD, and three of the patients had been infused. The two subjects with at least three months of follow-up data show a gradual increase in hemoglobin A containing $\beta^{A\text{-}T87Q}$ level post-infusion. The safety profile in the infused patients in the HGB-206 study is consistent with autologous transplantation and no drug product-related adverse events were observed as of November 17, 2015. Below is a table summarizing the preliminary clinical data from the HGB-206 study presented at the ASH annual meeting in December 2015.

Patient	1301	1303	1306
Enrollment age	25	42	20
CD34+ VCN	0.6/0.5	1.3	0.6
CD34+ cell count	2.6	2.8	2.1
($x10^6$/kg)			
Days to neutrophil engraftment	Day +18	Day +16	--
HbA^{T87Q}/total Hb (g/dL)	0.3 / 8.5	1.0 / 8.6	--
Last study follow up visit (months)*	3	4.5	<1

* Last scheduled study visit for which results were available as of November 17, 2015.

The safety profile in the infused patients in the HGB-206 Study is consistent with autologous transplantation and no drug product-related grade 3 or greater adverse events observed as of November 17, 2015.

It should be noted that these data presented above are current as of the dates presented, are preliminary in nature and the HGB-206 study is not complete. There is limited data concerning long-term safety and efficacy following treatment with our LentiGlobin drug product. These data may not continue for these subjects or be repeated or observed in ongoing or future studies involving our LentiGlobin product candidate, including the HGB-205 study, the Northstar Study, or the HGB-206 study in severe SCD. It is possible that subjects for whom transfusion support has been reduced or eliminated may receive transfusion support in the future.

Our planned Phase III clinical studies for TDT

We have discussed the designs of two planned Phase III clinical studies of our LentiGlobin product candidate with the FDA and EMA. Our planned HGB-207 study will be a single-dose, open-label, non-randomized, global, multi-site Phase III clinical study to evaluate the safety and efficacy of the LentiGlobin product candidate to treat TDT. Our HGB-207 study is currently planned to enroll up to 15 adult and adolescent subjects. Participants in this study must

have a diagnosis of TDT and have non-$^{0}/_{0}$ genotypes. They must also be eligible for HSCT. Efficacy in this study will be evaluated primarily by 12 consecutive months of transfusion independence. Subjects will be monitored by regular screening. Each subject will remain in the study for approximately 24 months of follow-up and will then be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond 24 months. As required of all gene therapy clinical trials, we filed the clinical study protocol for our HGB-207 study with the Recombinant DNA Advisory Committee, or RAC, convened by the National Institutes of Health, or NIH. The RAC notified us that our HGB-207 study does not require an in-depth review or public RAC discussion. We intend to begin initiating our HGB-207 study in late 2016.

We are also considering initiating an additional Phase III clinical study in pediatric subjects who have a diagnosis of TDT, which we have referred to as the HGB-208 study. Based upon the proposed protocol for the HGB-208 study filed with the RAC, the RAC notified us in 2015 that it recommends delay of the initiation of a Phase III pediatric clinical study for one to two years. We intend to continue to work closely with regulatory authorities and our clinical study sites to evaluate our plans for both the HGB-207 study and for studying our LentiGlobin product candidate in pediatric subjects.

Our Lenti-D product candidate opportunity

Adrenoleukodystrophy

Adrenoleukodystrophy is a rare X-linked, inherited, neurological disorder that is often fatal. ALD is caused by mutations in the ABCD1 gene which encodes for a protein called the ALD protein, or ALDP, which plays a critical role in the breakdown and metabolism of very long-chain fatty acids, or VLCFA. Without functional ALDP, VLCFA accumulate in cells throughout the body, including in the brain, spinal cord and adrenal glands. The build-up of VLCFAs causes damage to the myelin sheath, a protective and insulating membrane that surrounds nerve cells, in the brain. This damage can result in decreased motor coordination and function, visual and hearing disturbances, the loss of cognitive function, dementia, seizures, and other complications, including death. The worldwide incidence rate for ALD is approximately one in 17,000 newborns.

ALD is divided into various sub-segments with two main phenotypes that impact brain function:

- CALD (Cerebral adrenoleukodystrophy): The most severe form of ALD is CALD. CALD is characterized by progressive destruction of myelin, leading to severe loss of neurological function and eventual death. About 30-40% of patients with ALD are young boys affected by CALD. In boys affected by CALD, learning and behavioral problems are often observed in mid-childhood between the ages of 3 and 15 years (median age 7). In the absence of intervention, boys affected by CALD typically experience rapid degeneration into vegetative state, and ultimately death within a decade of diagnosis.
- AMN (Adrenomyeloneuropathy): AMN, which typically develops in adults aged 21 years and older, is the most common neurological form of ALD. All patients with AMN present with more slowly progressive symptoms resulting from (non-inflammatory) disruption of the axons (which are a fundamental component of the central nervous system that allows nerve signals to be transmitted in the spinal cord). Approximately 45-60% of patients diagnosed with AMN converts to CALD during their lifetime after age 18.

Limitations of current treatment options

There is a clear unmet medical need for patients with the cerebral phenotype of ALD. Currently, the only effective treatment option for patients with CALD is allogeneic HSCT. In this procedure, the patient is treated with HSCs containing a functioning copy of the gene contributed by a donor other than the patient. Allogeneic HSCT has also been shown to have potential clinical benefit in CALD affecting both children and adults.

Allogeneic HSCT is preferably performed early in the course of the disease, ideally using an unaffected matched sibling HSC donor to minimize complications. However, the majority of allogeneic HSCT procedures for CALD are carried out with non-sibling matched donor cells, partially matched related or unrelated donor cells including umbilical cord blood cells because a matched sibling donor is not available in most cases. The difficulty of finding a suitable sibling-matched donor is one of the primary drawbacks of this approach. Complications of allogeneic HSCT include a significant risk of morbidity and mortality related to immunosuppressive medications, graft failure, GVHD and opportunistic infections, particularly in patients who undergo non-sibling-matched allogeneic HSCT.

Moreover, of the approximately 80 boys who are born with CALD each year in the United States and European Union, we estimate that approximately 50% may have disease so advanced at the time of diagnosis that a beneficial outcome from treatment would be unlikely. This is attributed to rapid disease progression and difficulty with early diagnosis, as the initial presentation of the signs and symptoms of CALD are frequently misdiagnosed. Newborn screening through a simple and inexpensive blood test can enable earlier detection of CALD and is available in several states. Based in part on the fact that several states have approved or are currently considering universal newborn screening for ALD, it is our expectation that newborn screening will be broadly adopted in the United States within the next five years, and potentially elsewhere, providing for the opportunity to identify more boys for proactive monitoring of disease symptoms and early disease intervention.

Our Lenti-D product candidate

We are developing our Lenti-D product candidate as a potential one-time treatment to halt the progression of CALD. Our approach involves the ex vivo insertion of a functional copy of the ABCD1 gene via an HIV-1 based lentiviral vector into the patient's own HSCs to correct the aberrant expression of ALDP in patients with CALD. Upon successful engraftment of our Lenti-D product candidate, we expect that microglia in the brain derived from the transduced HSCs will correct the metabolic abnormalities resulting from excess VLCFA and stabilize the demyelination and cerebral inflammation characteristic of CALD.

We treated the first subject in the Starbeam Study in the United States in 2013. If successful, and pending further discussion with the regulatory authorities, the results from the Starbeam Study could potentially form the basis of a BLA submission to the FDA and an MAA to the EMA for this product candidate. However, there can be no assurance that the FDA and the EMA will not require additional studies before the approval of a BLA or MAA, respectively. The FDA has advised us that the Starbeam Study may not be deemed to be a pivotal study or may not provide sufficient support for a BLA submission. The FDA normally requires two pivotal

clinical studies to approve a drug or biologic product, and thus the FDA may require that we conduct additional clinical studies of Lenti-D prior to a BLA submission. Lenti-D has been granted Orphan Drug status by the FDA and EMA for adrenoleukodystrophy.

Clinical development of our Lenti-D product candidate

Completed non-interventional retrospective study (the ALD-101 Study)

Due to the rarity of CALD, allogeneic HSCT has historically not been subject to extensive analysis in controlled clinical studies, so progression of the disease and the efficacy and safety profile of allogeneic HSCT is largely absent from the current scientific literature. In order to properly design future clinical studies of Lenti-D and interpret the efficacy and safety results thereof, at the recommendation of the FDA, we performed a non-interventional retrospective data collection study to assess the natural course of disease in CALD patients that were left untreated, which we refer to as the untreated group or cohort, in comparison to the efficacy and safety data obtained from patients that received allogeneic HSCT, which we refer to as the treated cohort. A non-interventional retrospective data collection study involves an examination of historical clinical records from patients in order to assess the typical course of the condition and the efficacy and safety of treatment options. In the study, we collected survival, functional and neuropsychological assessments and neuroimaging data for both treated and untreated patients, as available; however, given the retrospective nature of the study, we were not able to collect comprehensive data for all subjects.

For this study, we collected data from four U.S. sites and one French site on a total of 137 subjects, 72 of whom were untreated and 65 of whom were treated with allogeneic HSCT. To our knowledge, the ALD-101 Study is the most comprehensive study ever conducted to characterize clinical outcomes in untreated and allogeneic HSCT-treated CALD patient populations.

Three primary clinical measurements of CALD disease progression

The findings from the ALD-101 Study suggest that, although there are a wide number of cognitive, behavioral, functional and radiological modalities utilized to assess patients with CALD, three are utilized most widely and consistently:

- The Neurological Function Score (NFS). The NFS is a 25-point neurological function score that assesses fifteen neurological abnormalities typically caused by ALD. These neurological abnormalities are summarized below:

Symptoms	Score
Loss of communication*	3
No voluntary movement*	3
Cortical blindness*	2
Tube feeding*	2
Wheelchair required*	2
Total incontinence*	2
Swallowing/other CNS dysfunctions	2
Spastic gait (needs assistance)	2
Hearing/auditory processing problems	1
Aphasia/apraxia	1
Visual impairment/fields cut	1
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Episodes of incontinency	1
Nonfebrile seizures	1

Total	25

*Major Functional Disabilities (MFDs)

Among the 15 functional domains in the NFS scale, we consider six to be of particular clinical importance because when these neurological abnormalities occur, a patient's ability to function independently is severely compromised. These particular deficiencies, which we define as Major Functional Disabilities, or MFDs, are loss of communication, complete loss of voluntary movement, cortical blindness, requirement for tube feeding, wheelchair dependence and total incontinence.

- The Loes score. The Loes score is a 34-point scale specifically designed to objectively measure the extent of central nervous system disease burden based on brain magnetic resonance imaging, or MRI, studies. The Loes score measures the extent and location of brain abnormalities such as the presence of white matter changes, degree of demyelination and the presence of focal or global atrophy. A Loes score of one-half or more (i.e., the presence of any such abnormalities) indicates the cerebral form of the disease, and patients with a Loes score of 10 or more generally are not considered to be good candidates for allogeneic HSCT due to the advanced stage of the disease.

- Gadolinium enhancement. One of the hallmarks of inflammatory disease in ALD patients is the presence of a compromised blood-brain barrier behind the leading edge of demyelinating lesions in the brain. This can be assessed using a contrast agent called gadolinium in brain MRI studies. Evidence of gadolinium enhancement in the brain in a MRI study, referred to by clinicians as a gadolinium positive result, suggests that neuroinflammation is present and the blood-brain barrier has been compromised, which in published studies has been shown to be a predictive biomarker of ALD disease progression.

Summary of findings

Key findings from the ALD-101 Study are summarized below:

- Untreated, patients with CALD progress to dismal outcomes. In the untreated cohort, the median overall survival was 92 months (7.7 years) and the estimated probability of survival at five years was 55%. Although informative, survival data must be considered in light of the fact that supportive measures may be used to sustain life after progression to a vegetative state.
- Baseline disease severity, as assessed by NFS and Loes scores, were good predictors of survival. In both the untreated and treated cohorts, significantly lower mortality rates were seen in patients with lower baseline NFS and Loes scores than in those with higher scores.

	Mortality Rate*			
			Loes ³ 0.5	
	NFS£ 1	NFS > 1	£ 9	Loes > 9
Untreated Cohort	42%	85%	44%	76%
Treated Cohort	12%	29%	13%	28%

* Mortality rate determined by the number of deaths that occurred at any time through the observation period post-CALD diagnosis.

As a consequence of this observation, and consistent with entry criteria that have been used in studies of allogeneic HSCT, the entry criteria for the Starbeam Study excludes subjects with evidence of advanced disease on NFS and Loes score to prevent enrollment of subjects whose disease would be expected to progress to a poor outcome despite treatment.

- MFDs occurred in the majority of the untreated cohort who showed evidence of gadolinium enhancement in brain MRI. The majority of untreated subjects (67%) had progressive disease resulting in premature MFD or death during the study period, with 91% (19/21) of gadolinium positive subjects dying or having an MFD during the study period.
- Allogeneic HSCT was associated with disease stabilization. Despite the significant risk of morbidity and mortality associated with allogeneic HSCT, successful transplantation was shown to provide clinically meaningful benefit to patients with CALD, particularly those with early-stage disease. Of the subjects who were evaluable at 24 months post-allogeneic-HSCT, 49% (N=51) of the allogeneic-HSCT cohort remained MFD-free. Allogeneic HSCT was also associated with resolution of gadolinium enhancement. Of those patients who would meet eligibility criteria for the Starbeam study (baseline NFS of zero or one, gadolinium-positive prior to allogeneic HSCT, baseline Loes between 0.5 and nine, inclusive and did not have a matched sibling), four of 17 (24%) patients developed an MFD within 24 months post-allogeneic HSCT.
- Consistent with published literature, allogeneic HSCT, particularly with unmatched/unrelated donors, was associated with clinically significant morbidity and mortality.
- Morbidity: Post-allogeneic HSCT, engraftment failure occurred in 12 of 65 (19%) patients, 10 of whom (83%) were transplanted with unrelated donor cells. Despite prophylaxis, the GVHD rate was reported in 34 of 58 evaluable subjects (59%), including acute GVHD in 26 (45%) patients and chronic GVHD in 12 (19%) patients. Due to the requirement for myeloablation prior to HSCT, the occurrence of GVHD and the requirement for immunosuppressive therapy post-allogeneic HSCT, allogeneic HSCT is associated with a substantial risk of life-threatening infection. Infections were the most commonly reported serious adverse event, with at least one serious infection reported in 19

(29%) patients post-allogeneic HSCT. The substantial morbidity associated with allogeneic HSCT for CALD supports evaluating Lenti-D in the Starbeam Study as an alternative therapeutic option that is expected to avoid the issues of immune incompatibility seen with allogeneic HSCT.

- Mortality: Post-allogeneic HSCT, the 100-day mortality rate was 8% and the overall one-year mortality rate was 19%. The estimated probability of two and five year survival rates post-allogeneic HSCT were 82% and 74%, respectively. As anticipated from the published literature, analysis of survival by type of donor (matched sibling versus other) showed that the proportion of deaths through the observation period post- allogeneic HSCT was lower in matched-sibling donor cases than in other allogeneic HSCT cases. The majority of allogeneic HSCT patients (46 patients; 71%) were transplanted with unrelated donor cells given the limited availability of HLA-matched sibling donors. As a result of this analysis, we determined to exclude patients with a sibling-matched donor from the Starbeam Study.

We believe the results from the ALD-101 Study support the proposition that, while the approach of treating a patient with genetically corrected HSCs can stabilize the progression of disease in patients with CALD, there remains a significant unmet medical need for safer therapies, particularly for patients without the option of a sibling-matched donor. We believe that many of the issues that contribute to the mortality and morbidity associated with allogeneic HSCT could be avoided using a patient's own gene-modified HSCs. Importantly, the results from this study were also used to inform the criteria for patient and endpoint selection for our Starbeam Study.

Previous clinical experience with lentiviral gene therapy for CALD (the TG04.06.01 Study)

Between September 2006 and September 2010, four boys with a confirmed diagnosis of CALD were treated in Paris, France, in a Phase I/II study with autologous HSCs transduced ex vivo with a lentiviral vector carrying a functional ABCD1 gene before reinfusion. Short-term clinical data and biological experience with the first two treated boys was first reported in Science (2009).

The TG04.06.01 Study is sponsored by the institut national de la santé et de la recherche médicale (French Institute of Health and Medical Research), or Inserm, in Paris, and the lentiviral vector was supplied by a third party company not affiliated with bluebird bio. We are party to a strategic collaboration agreement with Inserm for the development of HSC gene therapies in this patient population, pursuant to which we are collaborating with Patrick Aubourg, the Principal Investigator of the TG04.06.01 Study.

In the TG04.06.01 Study, all four subjects had cerebral demyelinating lesions with Loes scores ranging from two to seven prior to treatment. Gadolinium contrast enhancement indicated that the lesions were active and inflammatory in all four subjects. At the time of enrollment, each subject had a normal neurologic examination with NFS equal to zero.

Below is a summary of the efficacy results for each of the four subjects in the TG04.06.01 Study as of March 2013:

- Subject One: Loes score stabilized at month 30 and remained stable through month 75.
- Subject Two: Loes score stabilized at month 30 and remained stable through month 64. Gadolinium enhancement was initially positive, resolved, reappeared in the parietal area and then resolved and has remained negative.
- Subject Three: Loes score stabilized at month 33 but gadolinium enhancement has persisted. Subject Three had active, progressive disease post-transplant resulting in the development of significant cognitive deficits with the loss of ability for new learning consistent with a frontal lobe syndrome, including the loss of spontaneous speech by month 33 and urinary incontinence. As of 54 months post-transplant, he had no further decline in NFS or Loes scores since his month 33 evaluation.
- Subject Four: Loes score stabilized at month 16 and remained stable at 24 months. Gadolinium enhancement disappeared 45 days post-transplant and was still not detectable at month 12.

We believe these efficacy results are consistent with outcomes that would be expected following successful allogeneic HSCT. All four boys were alive two years or more after treatment, while the ALD-101 Study would suggest an expected mortality rate of approximately 20% in the same two-year window post-allogeneic HSCT. As assessed by NFS and brain MRI, Subjects One, Two and Four showed encouraging evidence of disease stabilization. Additionally, gadolinium enhancement resolved in Subjects One, Two and Four, suggesting a reduction of neuroinflammation. These results also contrast with the natural history of disease in untreated patients, which is characterized by continuous and rapid progression of cerebral demyelination in the majority of cases, particularly those with gadolinium enhancement on brain MRI. All four subjects demonstrated some deterioration of neurologic function within the second year after transplant, which is expected as it is also seen following allogeneic HSCT. Although neurologic deficits have occurred in these subjects post-treatment, we are encouraged by the fact that neurologic disease stabilized in all four subjects.

Importantly, as of March 2013, there were no reported incidents of gene therapy-related safety concerns in the TG04.06.01 Study. In addition, none of these subjects experienced adverse events due to immune incompatibility issues typically associated with allogeneic HSCT, such as graft rejection or GVHD.

We believe the efficacy and safety results of the TG04.06.01 Study provided clinical proof-of-concept, as the lentiviral vector used in the study shares many features with our Lenti-D vector. In addition, the results of the TG04.06.01 Study were helpful in informing the design of our Starbeam Study. The design of the Starbeam Study is built upon the observations made in the TG04.06.01 Study, but will enroll a larger number of subjects, is a multi-site trial with a different primary endpoint and in consultation with experts in the field, and has a predefined criterion for clinical success. Additionally, with improvements we have introduced into the vector manufacturing and transduction processes, we expect to obtain a higher frequency of gene-modified HSCs in subjects treated in the Starbeam Study compared to what was achieved in the TG04.06.01 Study, which we believe should translate into improved clinical benefit by virtue of the increased expression of normally-functioning ALDP.

Phase II/III Starbeam clinical study

In October 2013, we treated the first subject in a Phase II/III clinical study, called the Starbeam Study, of our Lenti-D product candidate, to evaluate its safety and efficacy in subjects with CALD. In May 2015, we announced that we had achieved our initial enrollment target for the Starbeam Study with 18 subjects enrolled. The study is designed as a single-dose, open-label, non-randomized, international, multi-site Phase II/III study to test the safety and efficacy of our Lenti-D product candidate in preserving neurological function and stabilizing cerebral demyelination in subjects with CALD. Subjects will be followed for 24 months post-infusion under this protocol. In accordance with applicable guidance from the FDA and EMA, we will be monitoring study subjects in a separate long-term follow up protocol to evaluate safety for up to 15 years, and will also monitor efficacy endpoints to demonstrate a sustained treatment effect. In the study, subjects must be age seventeen years or younger with a confirmed diagnosis of active CALD, including elevated levels of plasma VLCFA, a brain MRI Loes score of 0.5 to nine, inclusive, evidence of gadolinium enhancement and an NFS £ one. Subjects with a willing, unaffected 10/10 HLA matched sibling HSCT donor will be excluded from the study.

We have defined the primary efficacy endpoint in the Starbeam Study as the proportion of subjects who have no MFDs, as measured by NFS, at 24 months (±two months) post-infusion. Secondary efficacy evaluations, in each case measured at 24 months (±two months) post-infusion, capture the key assessments of CALD disease status, including the change from baseline in NFS and Loes score, resolution of gadolinium enhancement on MRI and determination of MFD-free survival and overall survival. The sample size for this study was not determined by formal statistical methods, but we believe it may be sufficient to demonstrate a robust effect on the binary response endpoint, where a responder is defined as a subject with no MFD at 24 months (±two months) following treatment with Lenti-D drug product. Thus, we expect the FDA and EMA will make a qualitative assessment of the efficacy and safety data from this study to evaluate whether the results are sufficient to support a BLA or MAA filing.

Safety evaluations will be performed during the study and will include evaluation of the following: success and kinetics of HSC engraftment; incidence of transplant-related mortality; detection of vector-derived replication of the lentivirus; and characterization and quantification of events related to the location of insertion of the functional gene in target cells.

If successful, we believe that the results from the Starbeam Study could form the basis of a BLA and an MAA. However, given the current number of subjects and design of the study and the qualitative/subjective assessment of the data, there can be no assurance the FDA or EMA will not require one or more additional clinical studies as a precursor to a BLA application or an MAA, respectively. The FDA has advised us that the Starbeam Study may not be deemed to be a pivotal study or may not provide sufficient support for a BLA submission. The FDA normally requires two pivotal clinical studies to approve a drug or biologic product, and thus the FDA may require that we conduct additional clinical studies of our Lenti-D product candidate prior to a BLA submission.

The ALD-103 observational study

We are also conducting an observational study of subjects with CALD treated by allogeneic HSCT referred to as the ALD-103 study. This study will collect efficacy and safety outcomes data in patients who are undergoing allogeneic HSCT in a period that is contemporaneous with ALD-102. We anticipate that our Lenti-D product candidate safety and efficacy will be evaluated by the FDA and EMA in light of the data collected in the Starbeam Study as well as our retrospective ALD-101 study and our observational ALD-103 study.

Our Preclinical Research Opportunities in HSCs

We believe our current gene therapy platform will enable us to develop and test new vectors based on similar viral vector backbones that carry different gene sequences for other severe genetic diseases. In this way, we believe that we can advance products efficiently through preclinical into clinical development. We may consider research and

development programs targeting other monogenic, genetic diseases that involve cells derived from HSCs for use in the ex vivo setting. These programs may involve severe genetic and rare diseases that could be developed and potentially commercialized on our own.

In addition, we believe our expertise in lentiviral vector production and cell transduction also provides an opportunity to develop new lentiviral products for use in the in vivo setting. In this case, lentiviral vectors carrying certain gene sequences would be delivered directly to the disease site (e.g., to the brain, liver or eye) or into the bloodstream of the patient and, in each case, the vector would need to find the target cell in vivo and deliver the genetic material into those target cells. Although this represents a less controlled environment in which to transduce cells and deliver genetic material, we believe it opens up additional rare disease and large market indications where this approach is more appropriate for the disease and targeted cells.

Our T Cell-Based Immunotherapy Opportunity

We are engaging in the discovery and development of novel, disease-altering gene therapies in oncology. We believe that our gene therapy platform can be applied to genetically modify a patient’s own T cells to target and destroy cancer cells by recognizing specific cell surface proteins, in the case of chimeric antigen receptors, or CARs, or by recognizing specific protein fragments derived from

either intracellular or extracellular protein, in the case of T cell receptors, or TCRs. Since our collaboration arrangement with Celgene was announced in March 2013, we have worked collaboratively to discover, develop and commercialize CAR T cell product candidates in oncology. Our collaboration arrangement with Celgene was amended in June 2015 to focus on CAR T cell product candidates targeting BCMA, a cell surface protein that is expressed on normal plasma cells and on most multiple myeloma cells, but is absent from other normal tissues. In February 2016, we infused the first subject in our Phase I clinical study of our bb2121 product candidate, the first product candidate from this collaboration. Celgene has exercised its option to exclusively license our bb2121 product candidate, while we have retained an option to co-develop and co-promote this product candidate. In June 2015, we announced a strategic collaboration with Kite Pharma, Inc. to jointly develop and commercialize second-generation TCR product candidates against the human papillomavirus type 16 E6 (HPV-16 E6) oncoprotein using our lentiviral and gene editing technologies. We are also independently researching and developing other CAR T product candidates against a variety of targets relevant to both hematologic and solid tumors.

Immune System and T Cells

The immune system recognizes danger signals and responds to threats at a cellular level. It is often described as having two arms. The first arm is known as the innate immune system, which recognizes non-specific signals of infection or abnormalities as a first line of defense. The innate immune system is the initial response to an infection, and the response is the same every time regardless of prior exposure to the infectious agent. The second arm is known as the adaptive immune system, which is composed of highly specific, targeted cells and provides long-term recognition and protection from infectious agents and abnormal processes such as cancer. The adaptive immune response is further subdivided into humoral, or antibody based, and cellular, which includes T cell-based immune responses.

The most significant components of the cellular aspect of the adaptive immune response are T cells, so called because they generally mature in the thymus. T cells are involved in both sensing and killing infected or abnormal cells, as well as coordinating the activation of other cells in an immune response. These cells can be classified into two major subsets, CD4+ T cells and CD8+ T cells, based on cell surface expression of the CD4 or CD8 glycoproteins. Both subsets of T cells have specific functions in mounting an immune response capable of clearing an infection or eliminating cancerous cells. CD4+ T cells, or helper T cells, are generally involved in coordinating the immune response by enhancing the activation, expansion, migration, and effector functions of other types of immune cells. CD8+ T cells, or cytotoxic T cells, can directly attack and kill cells they recognize as infected or otherwise abnormal, and are aided by CD4+ T cells. Both types of T cells are activated when their T cell receptor recognizes and binds to a specific protein structure expressed on the surface of another cell. This protein structure is composed of the major histocompatibility complex, or MHC, and a small protein fragment, or peptide, derived from either proteins inside the cell or on the cell surface. Circulating CD4+ and CD8+ T cells survey the body differentiating between MHC/peptide structures containing “foreign” peptides and those containing “self” peptides. A foreign peptide may signal the presence of an immune threat, such as an infection or cancer, causing the T cell to activate, recruit other immune cells, and eliminate the targeted cell.

Although the immune system is designed to identify foreign or abnormal proteins expressed on tumor cells, this process is either ineffective or defective in cancer patients. The defective process sometimes occurs when cancer cells closely resemble healthy cells and go unnoticed or if tumors lose their MHC protein expression. Additionally, cancer cells employ a number of mechanisms to escape immune detection to suppress the effect of the immune response. Some tumors also encourage the production of cells that suppress the immune response, such as regulatory T cells that block cytotoxic T cells that would normally attack the cancer.

History of Cancer Immunotherapy

Cancer has historically been treated with surgery, radiation, chemotherapy and hormone therapy. More recently, advances in understanding of the immune system's role in cancer have led to immunotherapy becoming an important treatment approach. Cancer immunotherapy began with treatments that nonspecifically activated the immune system and had limited efficacy and/or significant toxicity. In contrast, new immunotherapy treatments can activate specific, important immune cells, leading to improved targeting of cancer cells, efficacy, and safety. Within the immunotherapy category, treatments have included cytokine therapies, antibody therapies, and adoptive cell transfer therapies.

In 1986, interferon-a became the first cytokine approved for cancer patients. In 1992, interleukin-2, or IL-2, was the second approved cytokine in cancer treatment, showing efficacy in melanoma and renal cell cancer. IL-2 does not kill cancer cells directly, but instead nonspecifically activates and stimulates the growth of the body's own T cells which then combat the tumor. Although interferon-a, IL-2, and subsequent cytokine therapies represent important advances in cancer treatment, they are generally limited by toxicity and can only be used in a limited number of cancers and patients.

Cytokine-based therapies set the stage for immunotherapy, and antibody therapies represented the next significant advance, with targeted specificity and a generally better-tolerated side effect profile. Monoclonal antibodies, or mAbs, are designed to attach to proteins on cancer cells, and once attached, the mAbs can make cancer cells more visible to the immune system, block growth signals of cancer cells, stop new blood vessels from forming, or deliver radiation or chemotherapy to cancer cells. The first FDA-approved

mAb specifically for cancer was rituximab in 1997, and since then, many other antibodies have received approval, including trastuzumab, bevacizumab, alemtuzumab, cetuximab, and panitumumab. More recently, antibodies have been conjugated with cytotoxic drugs to increase activity. The first approved antibody drug conjugate was gemtuzumab ozogamicin in 2000, followed by brentuximab vedotin in 2011 and trastuzumab emtansine in 2013.

The next important advance has been the development of antibodies that target T cell checkpoint pathways, which are means by which cancer cells are able to inhibit or turn down the body's immune response to cancer. These treatments have shown an ability to activate T cells, shrink tumors, and improve patient survival. In 2011, ipilimumab became the first checkpoint inhibitor approved by the FDA. Recent clinical data from checkpoint inhibitors such as nivolumab and pembrolizumab have confirmed both the approach and the importance of T cells as promising tools for the treatment of cancer.

Despite these many advances, a significant unmet need in cancer still persists. We believe that the use of human cells as therapeutic entities to re-energize the immune system will be the next significant advancement in the treatment of cancer. These cellular therapies may avoid the long-term side effects associated with current treatments and have the potential to be effective regardless of the type of previous treatments patients have experienced. We are developing CAR and TCR-based approaches using our lentiviral vector gene transfer technology and experience in order to specifically and directly deliver a payload of potent anti-cancer agents to T cells, which may give them the ability to kill the cancer cells.

Our CAR and TCR T Cell Technologies

Like our programs for HSCs, our T cell-based immunotherapies use a customized lentiviral vector to alter T cells ex vivo, or outside the body, so that the T cells can recognize specific proteins or protein fragments on the surface of cancer cells in order to kill these diseased cells. T cells that have been genetically-engineered to make CAR or TCRs are designed to help a patient's immune system overcome survival mechanisms employed by cancer cells. CAR T cell technology directs T cells to recognize cancer cells based on expression of specific cell surface antigens, whereas TCR T cell technology provides the T cells with a specific T cell receptor that recognizes protein fragments derived from either intracellular or extracellular proteins.

With both our CAR and TCR T cell technologies, we harvest a patient's white blood cells in a process called leukapheresis, activate certain T cells to grow and then the gene sequences for the CAR or TCR construct are transferred into the T cell DNA using a lentiviral vector. The number of cells is expanded until it reaches the desired dose. These genetically engineered cells, which will express the receptors that can recognize the specific proteins that are characteristic of specific cancers, are then infused back into the patient. Our entire T cell engineering process is rapid (complete in around ten days) and manufactures modified T cells in a sterile closed system. When the engineered T cell is returned to the cancer patient, it engages the target protein on the cancer cell, triggers a series of signals that result in tumor cell killing through the production of anti-cancer cytokines, and undergoes multiple rounds of cell division to greatly expand the number of these anti-cancer T cells. These engineered T cells have the natural "auto-regulatory" capability of normal T cells and once the tumor cells containing the target antigen are destroyed, the engineered T cells decrease in number, but with the potential to leave a smaller number of T cells in the body as a form of immune surveillance against potential tumor regrowth. The genetically-engineered T cells are designed to supplement a patient's immune system and can be further engineered to overcome immune evasion mechanisms employed by cancer cells.

Our CAR and TCR T cell technologies also bring genomic engineering tools to the immunotherapy field. Using our gene editing technology, we have a number of additional options to manipulate the genome of the cancer patient's T

cells to further increase the specificity of the anti-tumor activity and to potentially make these cells even more potent. Specificity and potency are essential to the development of T cell therapies that can effectively treat solid tumor cancers such as breast, lung and colon cancer. Our cancer immunotherapy research group is staffed by scientists drawn from both industry and academic research centers that have pioneered the field of T cell therapy. This team is focused on the next generation of T cell engineering to discover and develop T cell product candidates to treat a variety of liquid and solid tumor malignancies.

Our CAR T cell product candidate - bb2121

We are developing bb2121, our first CAR T cell product candidate, as a potential treatment for multiple myeloma by binding to BCMA, a cell surface protein expressed on cancer cells. Multiple myeloma is a hematologic malignancy that develops in the bone marrow in which normal antibody-producing cells transform into myeloma. The growth of the cancer cells in the bone marrow blocks production of normal blood cells and antibodies, and also causes lesions that weaken the bone. According to the National Cancer Institute, more than 26,000 cases of multiple myeloma are expected in the United States in 2015. BCMA is expressed on normal plasma cells and on most multiple myeloma cells, but is absent from other normal tissues. We believe BCMA presents an attractive immunotherapeutic target for our technology for a number of reasons. In a preclinical BCMA multiple myeloma xenograft model, a single intravenous administration of bb2121 anti-BCMA CAR T cells resulted in rapid and sustained elimination of the tumors with 100 percent survival, while a month-long course of anti-myeloma therapy bortezomib only delayed tumor growth. In December 2015, researchers from the NIH announced promising clinical data in multiple myeloma with an anti-BCMA CAR T cell therapy that established clinical proof-of-concept for the BCMA target using a gamma-retroviral vector.

Our product candidate bb2121 is the result of our multi-year collaboration with Celgene and in February 2016, Celgene has exercised its option to exclusively develop and commercialize our bb2121 product candidate following the completion of the ongoing CRB-401 Phase I study. We retain an option to co-develop and co-commercialize this product candidate, as described more fully below under "Strategic collaborations—Our strategic alliance with Celgene."

The CRB-401 clinical study for relapsed/refractory multiple myeloma

In February 2016, we treated the first subject in our Phase I clinical study (CRB-401) to examine the safety and efficacy of our bb2121 product candidate in patients with relapsed/refractory multiple myeloma. The study is a single-dose, open-label, non-randomized, multi-site Phase I clinical study in the United States to determine the maximally tolerated dose and recommended Phase II dose. We expect that up to 40 patients will be enrolled in the CRB-401 study. In order to be eligible for this study, patients must have received 3 prior regimens, including a proteasome inhibitor (bortezomib or carfilzomib) and immunomodulatory agent (lenalidomide or pomalidomide). Following screening, enrolled subjects will undergo a leukapheresis procedure to collect autologous T cells for manufacturing our bb2121 drug product. Following manufacture of our bb2121 drug product, subjects will receive one cycle of lymphodepletion prior to bb2121 infusion.

Our TCR product candidate

In collaboration with Kite Pharma, Inc., we are co-developing and, if approved, co-commercializing, second generation TCR T cell-based therapies directed against an HPV-16 E6 antigen relating to certain cancers associated with the human papillomavirus, or HPV. HPV is the most common viral infection of the reproductive tract, with two viral strains, HPV type 16 and HPV type 18, believed to cause 70% of cervical cancers and precancerous cervical lesions, as well as other urogenital cancers. There were over 500,000 new cases and about 270,000 deaths attributable to cervical cancer worldwide in 2012. Additionally, HPV infection has become established as an etiologic risk factor for oropharyngeal head and neck cancers. The incidence of HPV-associated oropharyngeal cancers has been increasing for at least the past decade, and recent studies show that about 70 percent of oropharyngeal cancers may be linked to HPV. According to the Centers for Disease Control, there are over 12,000 new cases of oropharyngeal cancers in the United States a year, of which an estimated 7,500 new cases are attributable to HPV-16. Kite is currently conducting a Phase I/II study of a gamma-retroviral vector-based first generation TCR gene therapy directed against an HPV-16 E6 antigen that is not the subject of this collaboration. Our collaboration with Kite will leverage our lentiviral vector gene transfer platform in combination with gene editing technology. Kite will lead the program in the United States and we will have the option to lead the program in the European Union. Both companies will share overall costs, including research and development and sales and marketing expenses, and profits will be equally split between the companies. Additionally, Kite will have a co-promotion option in the European Union, and we will have a co-promotion option in the United States.

Our other preclinical research opportunities in T cell-based immunotherapy

We are pursuing multiple programs that leverage the unique properties of lentiviral vectors to target T cells as a therapy for various cancers. This represents a direct application of our expertise in gene therapy and our capabilities, know-how and patents associated with lentiviral gene therapy and gene editing for ex vivo applications. We are also independently researching and developing other CAR-T product candidates against a variety of targets relevant to both hematologic and solid tumors.

Our Gene Editing Opportunity

In June 2014, we acquired Pregenen, a privately-held biotechnology company headquartered in Seattle, Washington. Through the acquisition, we obtained rights to Pregenen's gene editing technology platform and cell signaling technology, and have integrated these technologies and research team and expanded its research efforts. We are focused on utilizing homing endonuclease and megaTAL gene editing technologies in a variety of potential applications and disease areas, including for oncology and hematology. Homing endonucleases and MegaTALs are novel enzymes that provide a highly specific and efficient way to modify the genome of a target cell to potentially treat a variety of diseases.

All of the gene-editing technologies currently being explored by the pharmaceutical industry, including zinc finger nucleases, CRISPR/Cas9, and TALENs, share common features of a DNA binding domain and a DNA cleavage domain. They all differ in specificity, size, ease of delivery and as naturally occurring versus engineered nucleases. Homing endonucleases and megaTALs are based on a naturally-occurring class of DNA cleaving enzymes that function as monomeric proteins able to bind DNA in a sequence-specific manner and cleave their target site. We believe there are multiple advantages of homing endonucleases and MegaTALs compared to other gene editing technologies, most notably: they are highly specific and efficient in cutting DNA and their compact size simplifies delivery to therapeutically relevant cell types. We are using our gene editing platform, along with collaborations with multiple academic institutions, to potentially discover and develop next generation versions of our current ex vivo gene therapy product candidates, and to potentially expand into new disease indications.

Manufacturing

Our gene therapy platform has two main components: lentiviral vector production and the target cell transduction process, which results in drug product.

Our lentiviral manufacturing process

Our lentiviral vectors are assembled using a human cell line called HEK293T. The HEK293T cells are maintained in disposable flasks until sufficient cell mass has been generated to fill approximately 40 ten tray cell factories, or TTCFs, then transferred and allowed to adhere to the bottom of the trays. Adherent cells are transfected with multiple plasmids encoding all the genetic material required to assemble the lentiviral vector carrying the functional gene of interest. The transfected HEK293T cells then assemble our lentiviral vectors packaged with the functional gene of interest, which bud off into the cell culture media. The media containing the assembled vectors is harvested, purified, concentrated and formulated prior to freezing for storage. These finished lentiviral vectors are what is ultimately used to transduce the targeted cells isolated from the patient.

We believe that our lentiviral vectors have broad applicability, since the majority of the viral production system can remain the same, while we change only the therapeutic gene “cassette” depending on the disease. In other words, the vector “backbone” stays the same, while only the therapeutic gene and related sequences are changed. If we were to undertake drug development in an additional indication, we believe we could rapidly move forward using this lentiviral vector backbone and associated assays, simply by switching the therapeutic gene insert and associated control elements.

Although we intend to continue manufacturing our Lenti-D vectors in TTCFs, we are adapting our LentiGlobin and bb2121 vector production technology to scalable production systems with the potential to satisfy an increased number of subjects per run. So far, we have demonstrated successful production of LentiGlobin and bb2121 vectors on a small scale and are transferring the new process to a contract manufacturer to accommodate future demand for our drug candidates, if approved, in their current indications as well as those beyond our initial focus.

Our HSC transduction process—creating the gene-modified HSCs (our drug product)

The ultimate product of our manufacturing processes is the patient’s own gene-modified HSC cells, which we refer to as our drug product. The process for producing drug product for our HSC-based product candidates is as follows:

1. Selection: We extract HSCs from peripheral blood mononuclear cells obtained from the patient’s blood by apheresis (or alternatively, by bone marrow harvest) following mobilization via a colony stimulating factor. The process is carried out using existing hospital infrastructure and standard protocols currently in place for stem cell transplant procedures, with enhanced controls for extracting the cells to be used for making our drug product.

2. Pre-stimulation: The isolated HSCs are treated with a mixture of growth factors that help enable an efficient transduction process.
3. Transduction: The isolated, purified and pre-treated HSCs are exposed to our lentiviral vectors containing the appropriate functional gene and additional proprietary elements for a period of time to facilitate transduction and insertion of the therapeutic DNA into the genome of the target cells.
4. Final harvest: Once transduction is complete, the gene-modified HSCs are washed and re-suspended into cell culture media to remove any residual impurities. A portion of the harvested cells is removed for quality control release testing, which includes ensuring that transduction was successful and the functional gene delivered by the vector is adequately expressed by the target cells.
5. Formulation and freeze: The remaining cells are appropriately formulated and cryopreserved.

The final step is to return the gene-modified HSCs to the patient.

Our T cell transduction process—creating the gene-modified T cells (our drug product)

The ultimate product of our manufacturing processes is the patient's own gene-modified T cells, which we refer to as our drug product. The process for producing drug product for our T cell-based product candidates is as follows:

1. Leukapheresis: We collect white blood cells from the patient's blood through a process called leukapheresis. The process is carried out using existing hospital infrastructure and standard protocols currently in place for blood donation procedures, with enhanced controls for extracting the cells to be used for making our drug product.
2. Activation: The white blood cell mixture, which includes T cells, are treated with proprietary processes to enable an efficient transduction process.
3. Transduction: The isolated, purified and pre-treated T cells are exposed to our lentiviral vectors containing the appropriate functional gene for a period of time to facilitate transduction and insertion of the therapeutic DNA into the genome of the target cells.
4. Expansion: The transduced T cells are then expanded for a period of approximately one week to increase the number of gene-modified T cells.
5. Final harvest: The gene-modified T cells are washed and re-suspended into cell culture media to remove any residual impurities. A portion of the harvested cells is removed for quality control release testing, which includes ensuring that transduction was successful and the functional gene delivered by the vector is adequately expressed by the target cells.
6. Formulation and freeze: The remaining cells are appropriately formulated and cryopreserved.

The final step is to return the gene-modified T cells to the patient.

We rely exclusively on the use of third party manufacturing organizations to manufacture our LentiGlobin, Lenti-D and bb2121 vectors and drug product candidates, and do not own or operate any of our own facilities for these purposes. However, we believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to effectively oversee these contract manufacturing and testing activities, and to compile manufacturing and quality information for our regulatory submissions.

Strategic collaborations

Our objective is to develop and commercialize products based on the transformative potential of gene therapy to treat patients with severe genetic and rare diseases and cancer. To access the substantial funding and other resources required to develop and commercialize gene therapy products in these diseases, we have formed, and intend to seek other opportunities to form, strategic collaborations with third parties who can augment our industry leading gene therapy, T cell immunotherapy, lentiviral vector and gene-editing expertise. To date, we have focused on forging a limited number of significant strategic collaborations with leading pharmaceutical companies and academic research centers where both parties contribute expertise to enable the discovery and development of potential product candidates.

Our collaboration with Celgene

In March 2013, we announced a strategic collaboration with Celgene to discover, develop and commercialize novel disease-altering gene therapies in oncology, which was amended and restated in June 2015, and amended again in February 2016. The multi-year research and development collaboration focused on applying our expertise in gene therapy technology to CAR T cell-based therapies, to target and destroy cancer cells. Our collaboration now focuses exclusively on anti-BCMA CAR T product candidates. We advanced our development of our bb2121 product candidate, the first CAR product candidate from our collaboration with Celgene, into clinical trials in February 2016. We will also work collaboratively with Celgene on potential next-generation anti-BCMA product candidates under this collaboration.

Under the terms of the collaboration, for up to two product candidates selected for development under the collaboration, we are and will be responsible for conducting and funding all research and development activities performed up through completion of the initial Phase I clinical study, if any, of such product candidates, provided that Celgene has agreed to reimburse us a specified amount per patient in the event we and Celgene mutually agree to expand any Phase I clinical trial for any product candidate under the collaboration beyond a specified number of patients per clinical trial. This collaboration is governed by a joint steering committee, or JSC, formed by representatives from us and Celgene. The JSC, among other activities, reviews the collaboration program, reviews and evaluates product candidates and approves regulatory plans.

On a product candidate-by-product candidate basis, up through a specified period following enrollment for the first patient in an initial Phase I clinical study for such product candidate, we have granted Celgene an option to obtain an exclusive worldwide license to develop and commercialize such product candidate pursuant to a written agreement, the form of which we have already agreed upon. Effective as of February 2016, Celgene has exercised its option with respect to the bb2121 product candidate, and we have licensed to Celgene the exclusive worldwide license to develop and commercialize the bb2121 product candidate. We may elect to co-develop and co-promote the product candidate bb2121 and any other product candidates in the United States, provided that, if we do not exercise our option to co-develop and co-promote the product candidate bb2121 in-licensed by Celgene under the collaboration, then we will not be permitted to exercise our option to co-develop and co-promote any future product candidates under the collaboration.

In connection with its exercise of the option to exclusively in-license the bb2121 product candidate, Celgene will pay to us an option fee in the amount of $10.0 million. If Celgene elects to exercise its option to exclusively in-license any additional product candidates, it must pay us an additional $15.0 million per product candidate. In addition to the applicable option fees, Celgene must pay to us an additional fee in the amount of $10.0 million in the event we do not exercise our option to co-develop and co-promote that product candidate in the United States. In addition, for each product candidate that is in-licensed by Celgene, and for which we do not exercise our option to co-develop and co-promote in the United States, we will be eligible to receive up to $10.0 million in clinical milestone payments, up to $117.0 million in regulatory milestone payments and up to $78.0 million in commercial milestone payments. We will also be eligible to receive a percentage of net sales as a royalty in a range from the mid-single digits to low-teens. The royalties payable to us are subject to certain reductions, including for any royalty payments required to be made by Celgene to acquire patent rights, with an aggregate minimum floor. Celgene will assume certain development obligations and must report on their progress in achieving these milestones on a quarterly basis.

If we do elect to co-develop and co-promote the product candidate within the United States, we would share equally in all costs relating to developing, commercializing and manufacturing the product candidate within the United States and we would share equally in the United States profits. Additionally, if we elect to co-develop and co-promote a product candidate, then the milestones and royalties would decrease compared to those described above. Under this scenario, we would receive per product candidate up to $10.0 million in clinical milestone payments and outside of the United States, up to $54.0 million in regulatory milestone payments and up to $36.0 million in commercial milestone payments. In addition, to the extent any of the product candidates licensed by Celgene and co-developed and co-promoted by us are commercialized, we would be entitled to receive tiered royalty payments ranging from the mid-single digits to low-teens based on a percentage of net sales generated outside of the United States. The royalties payable to us are subject to certain reductions, including any royalty payments required to be made by Celgene to acquire patent rights, with an aggregate minimum floor.

If Celgene does not exercise its option with respect to any product candidate prior to expiration of the applicable option period, then we have the right to develop that product candidate outside the scope of the collaboration.

Celgene will be solely responsible for all costs and expenses of manufacturing and supplying any optioned product candidates. Subject to customary “back-up” supply rights granted to Celgene, we have the sole right to manufacture or have manufactured supplies of vectors and associated payloads manufactured for incorporation into the optioned

product candidate. Celgene would reimburse us for our costs to manufacture and supply such vectors and associated payloads, plus a modest mark-up.

We received an initial up-front payment of $75.0 million from Celgene in connection with the collaboration, plus an additional $25.0 million in connection with the amendment in June 2015. The collaboration term ends in June 2018. Either party may terminate the agreement upon written notice to the other party in the event of the other party's uncured material breach. Celgene may terminate the agreement for any reason upon prior written notice to us. If the agreement is terminated, rights to product candidates in development at the time of such termination will be allocated to the parties through a mechanism included in the agreement. In addition, if Celgene terminates the agreement for our breach, any then- existing co-development and co-promotion agreement will be automatically terminated and replaced with a license agreement for such product candidate and any amounts payable by Celgene under any then-existing product license agreements will be reduced.

Baylor College of Medicine

Simultaneous with entering into the collaboration agreement with us, Celgene entered into a strategic collaboration with the Baylor College of Medicine, or Baylor, to discover, develop and commercialize CAR T cell products. We are not a party to this collaboration agreement, although, by virtue of our agreements with Celgene, the joint steering committee under the Baylor-Celgene collaboration agreement will include representatives selected by us, together with representatives selected by each of Celgene and Baylor. Under our collaboration agreement with Celgene, we may develop product candidates covered by the intellectual property rights of Baylor in this field, which intellectual property rights would be in-licensed by Celgene pursuant to its collaboration agreement with Baylor.

Our collaboration with Kite Pharma

In June 2015, we announced a strategic collaboration with Kite Pharma, Inc. to jointly develop and commercialize second generation TCR product candidates against the human papillomavirus type 16 E6, or HPV-16 E6, oncoprotein. The collaboration will apply our gene editing technology and expertise to modify certain genes to enhance T cell function. In addition, we will explore using lentiviral vectors to optimize delivery of HPV-16 E6 TCRs in patient T cells. Kite will lead the program in the United States, and we will have the option to lead the program in the European Union. Both companies will share overall costs, including research and development, and sales and marketing expenses and profits will be equally split between the companies. Additionally, Kite will have a co-promotion option in the European Union, and we will have a co-promotion option in the United States.

Intellectual property

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy that may be important for the development of our business. We additionally rely on regulatory protection afforded through orphan drug designations, data exclusivity, market exclusivity, and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same.

We have developed or in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to the development and commercialization of gene therapy products. Our proprietary intellectual property, including patent and non-patent intellectual property, is generally directed to, for example, certain genes, transgenes, methods of transferring genetic material into cells, genetically modified cells, processes to manufacture our lentivirus-based product candidates and other proprietary technologies and processes related to our lead product development candidates. As of January 31, 2016, our patent portfolio includes the following:

- approximately 183 patents or patent applications that we own or have exclusively in-licensed from academic institutions and third parties related to lentiviral vectors and vector systems;

- approximately 70 patents or patent applications that we have non-exclusively in-licensed from academic institutions and third parties related to lentiviral vectors and vector systems;
- approximately 37 patents or patent applications that we own or have exclusively in-licensed from academic institutions and third parties, including eight that are co-owned with MIT, related to vector manufacturing or production;
- approximately eight patents or patent applications that have been non-exclusively in-licensed from academic institutions and third parties related to vector manufacturing or production;
- approximately 23 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from academic institutions and third parties related to therapeutic cellular product candidates;
- approximately 117 patents or patent applications that we own or have exclusively in-licensed from academic institutions and third parties related to oncology product candidates, including CAR T cell vector systems and manufacturing, T cell manufacturing, and therapeutic T cells;

- approximately 68 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from academic institutions and third parties related to gene editing compositions and methods; and
- approximately two patent applications that we have non-exclusively in-licensed from academic institutions and third parties related to gene editing compositions and methods.

Our objective is to continue to expand our portfolio of patents and patent applications in order to protect our gene therapy product candidates manufacturing processes. Examples of the products and technology areas covered by our intellectual property portfolio are described below. See also "—License agreements."

ß-thalassemia/SCD

The ß-thalassemia/SCD platform includes three patent portfolios, described below.

- Pasteur Institute. The Pasteur patent portfolio contains patent applications directed to FLAP/cPPT elements and lentiviral vectors utilized to produce our LentiGlobin product candidate for ß-thalassemia and SCD. As of January 31, 2016, we had an exclusive license to nine issued U.S. patents and one pending U.S. application. Corresponding foreign patents and patent applications include pending applications or issued patents in Australia, Canada, China, Europe, Hong Kong, Israel, and Japan. We expect the issued composition of matter patents to expire from 2019-2023 in the United States, and from 2019-2020 in the rest of the world (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2019-2020 (excluding possible patent term extensions). We expect the patents and patent applications in this portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2019-2020 (worldwide, excluding possible patent term extensions).
- RDF. The in-licensed patent portfolio from Research Development Foundation, or RDF, in part, contains patents and patent applications directed to aspects of our lentiviral vectors utilized to produce our LentiGlobin product candidate for ß-thalassemia and SCD. As of January 31, 2016, we had an exclusive license (from RDF) to seven issued U.S. patents and two pending U.S. applications related to our lentiviral vector platform. Corresponding foreign patents and patent applications related to our lentiviral vector platform include pending applications or issued patents in Canada, Europe, and Israel. We expect the issued composition of matter patents to expire from 2021-2027 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2021-2022 (excluding possible patent term extensions). We expect the patents and patent applications in this portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2021-2022 (worldwide, excluding possible patent term extensions).
- MIT/bluebird bio. The co-owned patent portfolio contains patents and patent applications directed to certain specific compositions of matter for lentiviral ß-globin expression vectors. As of January 31, 2016, we co-owned two issued U.S. patents and one pending U.S. application, as well as corresponding foreign patents issued in Europe and Hong Kong. We expect the issued composition of matter patents to expire in 2023 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2023 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2023 (worldwide, excluding possible patent term extensions). We note that we have an exclusive license to MIT's interest in this co-owned intellectual property.

Cerebral Adrenoleukodystrophy (CALD)

The CALD platform includes three patent portfolios, described below.

- Pasteur Institute. The in-licensed Pasteur patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce our Lenti-D product candidate for CALD.

- RDF. The in-licensed RDF patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce our Lenti-D product candidate for CALD.
- bluebird bio. The bluebird bio patent portfolio contains patent applications directed to compositions of matter for CALD gene therapy vectors and compositions and methods of using the vectors and compositions in cell-based gene therapy of adrenoleukodystrophy or adrenomyeloneuropathy. As of January 31, 2016, we owned two U.S. patent and one pending U.S. application and 17 pending corresponding foreign applications or issued patents. We expect the issued composition of matter patents for CALD gene therapy vectors to expire in 2032 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions). We

expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions).

Lentiviral platform (e.g., vectors, manufacturing, and cell therapy products)

The lentiviral platform, which is potentially applicable to the ß-thalassemia, SCD, CALD, oncology and other potential programs, includes three patent portfolios, described below.

- Pasteur Institute. The Pasteur patent portfolio contains the patents and patent applications described above.
- RDF. The in-licensed RDF patent portfolio contains the patents and patent applications described above.
- bluebird bio. Another component of the bluebird bio patent portfolio includes the vector manufacturing platform and is potentially applicable to the CALD, ß-thalassemia, SCD, oncology, and other programs. This portion of the portfolio contains patents and patent applications directed to improved methods for transfection and transduction of therapeutic cells. As of January 31, 2016, we owned 2 pending U.S. applications and 21 corresponding foreign patent applications. We expect composition of matter and method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2032 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions).

Oncology / T cell-based immunotherapy platform

Our lead T cell immunotherapy product candidate, bb2121, includes three patent portfolios, described below.

- Pasteur Institute. The Pasteur patent portfolio contains the patents and patent applications described above.
- bb2121 Candidate Licenses. We have in-licensed a patent portfolio that contains patents and patent applications directed to aspects of our oncology platform to produce lentiviral vectors for a CAR T cell therapy product directed against BCMA. As of January 31, 2016, we had a co-exclusive license to seven issued U.S. patents and three pending U.S. applications and 28 pending corresponding foreign applications and 36 issued corresponding foreign patents related to bb2121. We expect the issued patents to expire from 2020-2032 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2020-2032 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2020-2032 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2016, we have an exclusive license to one pending U.S. application and 19 corresponding foreign patent applications related to bb2121. We expect composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2033 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).
- bluebird bio. One aspect of the bluebird bio patent portfolio contains patent applications directed to certain specific compositions of matter for generating CAR T cells. As of January 31, 2016, we owned two pending U.S. provisional applications and six pending PCT applications. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2035 (worldwide, excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035 (worldwide, excluding possible patent term extensions).

Our oncology research program includes other patent portfolios, described below.

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RDF. The in-licensed RDF patent portfolio described above contains patents and patent applications that are also applicable to our oncology platform. In addition, the RDF portfolio contains additional patent applications directed to aspects of our oncology program. As of January 31, 2016, we had an exclusive license (from RDF) to one issued patent and one pending U.S. applications related to our oncology platform. We expect the issued patent to expire in 2021 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2021-2022 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2021-2022 (worldwide, excluding possible patent term extensions).

- bluebird bio. One aspect of the bluebird bio patent portfolio contains patent applications directed to certain specific compositions of matter for generating CAR T cells directed against various cancers. As of January 31, 2016, we owned two pending U.S. provisional applications. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2036 (worldwide, excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2036 (worldwide, excluding possible patent term extensions).
- T Cell Immunotherapy Product Candidate Licenses. We have in-licensed patents and patent applications that are directed to certain specific compositions of matter for generating CAR T cells directed against various cancers. As of January 31, 2016, we had a co-exclusive or exclusive license to two pending U.S. provisional applications related to one particular target antigen. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2036 (worldwide, excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2036 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2016, we have an exclusive license to one issued U.S. patent and ten corresponding foreign patents and two corresponding foreign patent applications to another particular target antigen. We expect the issued composition of matter patent to expire in 2036 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2036 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2036 (worldwide, excluding possible patent term extensions).

Gene editing platform (e.g., homing endonucleases, chimeric endonucleases, megaTALs, genetically modified cells)

The gene editing platform includes five patent portfolios, described below.

- Pasteur Institute. The Pasteur patent portfolio described above may contain patents and patent applications that are potentially applicable to our gene editing platform.
- RDF. The in-licensed RDF patent portfolio described above may contain patents and patent applications that are potentially applicable to our gene editing platform.
- Gene Editing License. We in-licensed patent portfolios that contain patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our ß-thalassemia, SCD, oncology and other programs. As of January 31, 2016, we had an exclusive/co-exclusive license to three issued U.S. patents and two pending U.S. applications and two corresponding foreign patents and nine corresponding patent applications related to our gene editing platform. We expect the issued composition of matter patents to expire in 2030 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2030 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2030 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2016, we had an exclusive license to one issued U.S. patent and one pending U.S. application and five corresponding foreign patents related to our gene editing platform. We expect the issued composition of matter patent to expire in 2031 in the United States (excluding possible patent term extensions) and in 2027 in the rest of the world. Further, we expect composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2027 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2027 (worldwide, excluding possible patent term extensions).

- Academic Gene Editing Licenses. We in-licensed patent portfolios from multiple academic medical centers, each portfolio containing patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our ß-thalassemia, SCD, oncology and other programs. As of January 31, 2016, we had an exclusive license to one issued U.S. patent and three pending U.S. applications and four corresponding foreign patents and four corresponding patent applications related to our gene editing platform. We expect the issued patent to expire in 2032 (excluding possible patent term extensions) in the U.S. and 2027-3032 in the rest of the world. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2027-2032 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2027-2032 (worldwide, excluding possible patent term

extensions). As of January 31, 2016, we also had a non-exclusive license to one pending U.S. provisional application and one pending PCT application related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2036 (worldwide, excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2036 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2016, we had an exclusive license to 2 pending U.S. applications and 19 corresponding pending foreign patent applications related to our gene editing platform. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2031-2033 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2031-2033 (worldwide, excluding possible patent term extensions). As of January 31, 2016, we also had an exclusive license to one pending U.S. application and 18 corresponding foreign patent applications related to our gene editing platform. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2033 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).

- bluebird bio. One aspect of the bluebird bio patent portfolio contains patent applications that are potentially applicable to certain aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our oncology and other programs. As of January 31, 2016, we co-owned (with Cellectis) two pending U.S. applications and ten corresponding pending foreign patent applications related to our gene editing platform. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2034 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2034 (worldwide, excluding possible patent term extensions).

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

The term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration of a U.S. patent as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Moreover, a patent can only be extended once, and thus, if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of a BLA, we expect to apply for patent term extensions for patents covering our product candidates and their methods of use.

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and third parties. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these

individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

License agreements

Inserm-Transfert

In May 2009, we entered into an exclusive license with Inserm-Transfert, which is a wholly-owned subsidiary of Institut national de la santé et de la recherche médicale, for use of certain patents and know-how related to the ABCD1 gene and corresponding protein, for use in the field of human ALD therapy. Inserm-Transfert is referred to herein as Inserm. The Inserm licensed patent portfolio includes one U.S. patent in force. This portfolio has no pending applications. Inserm retains the right to practice the intellectual property licensed under the agreement for educational, clinical and preclinical studies purposes.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our Lenti-D product candidate, we will be obligated to pay Inserm a percentage of net sales as a royalty for the longer of the life of any patents covering the product or 10 years from first commercial sale. This royalty is in the low single digits. The royalties payable to Inserm are subject to reduction for any third party payments required to be made, with a minimum floor in the low single digits.

We are required to use all commercially reasonable efforts to develop licensed products and introduce them into the commercial market as soon as practical, consistent with our reasonable business practices and judgment in compliance with an agreed upon development plan. We have assumed certain development, regulatory and commercial milestone obligations and must report on our progress in achieving these milestones on an annual basis.

We may unilaterally terminate the license agreement at any time. Either party may terminate the agreement in the event of the other party's material breach which remains uncured after 60 days of receiving written notice of such breach or in the event the other party become subject of a voluntary or involuntary petition in bankruptcy and such petition is not dismissed with prejudice within 120 days after filing. In addition, Inserm may terminate the license agreement in the event that we cannot prove within 60 days of written notice from Inserm that we have been diligent in developing the licensed products and introducing them into the commercial market.

Absent early termination, the agreement will automatically terminate upon the expiration of all issued patents and filed patent applications within the patent rights covered by the agreement or 10 years from the date of first commercial sale of a licensed product, whichever is later. The license grant ceases in connection with any such termination. The longest lived patent rights licensed to us under the agreement are currently expected to expire in 2016.

Institut Pasteur

We have entered into a license with Institut Pasteur for certain patents relating to the use of DNA sequences, lentiviral vectors and recombinant cells in the field of ex vivo gene therapy and CAR T cell-based therapy in a range of indications, excluding vaccinations. This agreement was amended twice in 2012, again in 2013 and most recently in 2015. The Institut Pasteur licensed patent portfolio includes at least 83 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration dates between 2019 and 2023. The license is exclusive for products containing human and non-human lentiviral vectors. Institut Pasteur retains the right, on behalf of itself, its licensees and research partners, to conduct research using the licensed intellectual property.

We have the right to grant sublicenses outright to third parties under the agreement. For the first sublicense including a product targeting -hemoglobinopathies (including TDT and severe SCD) or ALD (including CALD and AMN), we must pay Institut Pasteur an additional payment of €3.0 million. If we receive any income (cash or non-cash) in connection with sublicenses for products targeting indications other than -hemoglobinopathies (including TDT and severe SCD) or ALD (including CALD and AMN), we must pay Institut Pasteur a percentage of such income varying from low single digits if the sublicense also includes licenses to intellectual property controlled by us, and a percentage of sublicense income in the mid-range double digits if the sublicense does not include licenses to intellectual property controlled by us.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our LentiGlobin and Lenti-D product candidates, we will be obligated to pay Institut Pasteur a percentage of net sales as a royalty. This royalty varies depending on the indication of the product but in any event is in the low single digits. In addition, starting in 2016 we must make under this agreement an annual maintenance payment which is creditable against royalty payments on a year-by-year basis. If the combined royalties we would be required to pay to Institut Pasteur and third parties is higher than a pre-specified percentage, we may ask Institut Pasteur to re-negotiate our royalty rates under this relationship.

We are required to use all reasonable commercial efforts (as compared to a company of similar size and scope) to develop and commercialize one or more products in the license field and to obtain any necessary governmental approvals in respect of, and market the products in license field, if any. Additionally, we have assumed certain development and regulatory milestone obligations. We must report on our progress towards achieving these milestones on an annual basis. We may unilaterally terminate the license agreement at any time by sending Institut Pasteur 90 days prior written notice. Either party may terminate the license in the event of the other party's substantial breach which remains uncured after 60 days of receiving written notice of such breach. Institut Pasteur may also terminate the agreement in the event bankruptcy proceedings are opened against us and not dismissed within 60 days.

Absent early termination, the agreement will automatically terminate upon the expiration of the last licensed patents or five years after first market authorization of the first product, whichever occurs later. In the event the agreement is terminated, while the license grant would cease, we would retain the right to manufacture, import, use and sell licensed products for a certain period of time post-termination. In addition, our ownership stake in certain jointly made improvements covered by the licensed patents would survive termination of the agreement. The longest lived patent rights licensed to us under the agreement are currently expected to expire in 2023.

Stanford University

In July 2002, we entered into a non-exclusive license agreement with the Board of Trustees of the Leland Stanford Junior University, referred to herein as Stanford, which we amended and restated in April 2012. Under this agreement, we are granted a license to use the HEK293T cell line for any commercial or non-commercial use for research, nonclinical and clinical development purpose and human and animal gene therapy products.

We have the right to grant sublicenses outright to third parties under the agreement. For each such sublicense we grant, we must pay Stanford a fee (unless the sublicense is to a collaborating partner, contract manufacturer or contract research organization).

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our Lenti-D product candidate, we will be obligated to pay Stanford a percentage of net sales as a royalty. This royalty varies with net sales but in any event is in the low single digits and is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage which is less than one percent. Since April 2013, we have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.

We may unilaterally terminate the agreement by giving Stanford 30 days' written notice. Stanford may also terminate the license agreement if after 30 days of providing notice we are delinquent on any report or payment, are not using commercially reasonable efforts to develop, manufacture and/or commercialize one or more licensed products, are in material breach of any provision or provide any false report. Termination of this agreement may require us to utilize different cell types for vector manufacturing, which could lead to delays.

Absent early termination, the license will expire in April 2037. We may elect to extend the term for an additional 25 years so long as we have a commercial product on the market at that time and we are in material compliance with the license agreement.

Massachusetts Institute of Technology

In December 1996, we entered into an exclusive license with the Massachusetts Institute of Technology, referred to herein as MIT, for use of certain patents in any field. This license agreement was amended in December 2003, May 2004 and June 2011. The licensed patent portfolio includes at least 20 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2023. This license also has been amended to include a case jointly owned by MIT and us wherein we received the exclusive license to MIT's rights in this case. MIT retains the right to practice the intellectual property licensed under the agreement for noncommercial research purposes.

We have the right to grant sublicenses outright to third parties under the agreement. In the event we sublicense the patent rights, we must pay MIT a percentage of all payments we receive from by the sublicensee. This percentage varies from mid-single digits to low double digits.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our LentiGlobin product candidate, we will be obligated to pay MIT a percentage of net sales by us or our sublicensees as a royalty. This royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one-percent. In addition, we make under this agreement an annual maintenance payment which may be credited against the royalty payments.

We are required to use diligent efforts to market licensed products and to continue active, diligent development and marketing efforts for licensed products during the term of the agreement. We have assumed certain milestones with respect to raising capital investment and regulatory progress. We must report on our progress on achieving these

milestones on an annual basis.

We may unilaterally terminate the license agreement upon six months' notice to MIT. MIT may terminate the agreement if we cease to carry on our business, or in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment). In the event the agreement is terminated, while the license grant would cease, we would retain a right to complete manufacture of any licensed products in process and sell then-existing inventory. In addition, MIT would grant our sublicensees a direct license following such termination. With respect to jointly owned intellectual property, any termination would allow MIT to grant licenses to any third party to such intellectual property, without our approval, unless a sublicensee was already in place, in which case, MIT would grant our sublicensees a direct license.

Research Development Foundation

In December 2011, we entered into an exclusive license with RDF to use certain patents that involve lentiviral vectors. The RDF licensed patent portfolio includes at least 25 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date between 2021 and 2027. RDF retains the right, on

behalf of itself and other nonprofit academic research institutions, to practice and use the licensed patents for any academic, nonclinical research and educational purposes. We have the right to grant sublicenses outright to third parties under the agreement.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include both our Lenti-D and LentiGlobin product candidates, we are obligated to pay RDF a percentage of net sales as a royalty. This royalty is in the low single digits and is reduced by half if during the following ten years from the first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.

We are required to use commercially reasonable and diligent efforts for a company of our size and resources to develop or commercialize one or more licensed products, including our first licensed product by 2016 and a second licensed product by 2018. These diligence efforts include minimum annual royalty payments to RDF, which are creditable against earned royalties otherwise due to RDF, and payments upon regulatory milestones.

RDF may terminate the agreement in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment) or in the event we become bankrupt, our business or assets or property are placed in the hands of a receiver, assignee or trustee, we institute or suffer to be instituted any procedure in bankruptcy court for reorganization or rearrangement of our financial affairs, make a general assignment for the benefit of creditors, or if we or an affiliate or a sublicensee institutes any procedure challenging the validity or patentability of any patent or patent application within the licensed patents, the agreement will immediately terminate.

Absent early termination, the agreement will continue until its expiration upon the later of there being no more valid claims within the licensed patents or the expiration of our royalty obligations on licensed products that are subject to an earned royalty, if such earned royalty is based on the minimum 10-year royalty period described above. In the event the agreement is terminated, while the license grant would cease, RDF will grant our sublicensees a direct license. The longest lived patent rights licensed to us under the agreement are in one U.S. patent currently expected to expire in 2027.

Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. We face potential competition from many different sources, including larger and better-funded pharmaceutical and biotechnology companies. Not only must we compete with other companies that are focused on gene therapy products but any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future.

There are other organizations working to improve existing therapies or to develop new therapies for our initially selected indications. Depending on how successful these efforts are, it is possible they may increase the barriers to adoption and success for our LentiGlobin, Lenti-D and bb2121 product candidates, if approved and our preclinical T cell-based immunotherapy product candidates. These efforts include the following:

- ß-thalassemia: The current standard of care for the treatment of ß-thalassemia in the developed world is chronic blood transfusions to address the patient’s anemia. In addition, such patients often receive iron chelation therapy to help manage the iron overload associated with their chronic blood transfusions. We understand that established biopharmaceutical companies, such as Novartis AG and ApoPharma Inc., who provide the leading iron chelation therapy, are seeking to develop improvements to their product profile and accessibility. In addition, some patients with ß-thalassemia receive HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. Approaches to reduce the risk of complications from allogeneic HSCTs are under investigation, including BPX-501, a modified donor T cell therapy in an ongoing Phase I/II study being supported by Bellicum Pharmaceuticals, Inc. A number of different approaches are under investigation to improve treatment options,

including iron modulating agents and fetal hemoglobin regulators. There are also several different groups developing gene therapy approaches for ß-thalassemia. Some of these groups use a similar ex vivo autologous approach, but make use of different vectors and different cell processing techniques. These include: GlaxoSmithKline Plc, which has entered into an agreement with the San Raffaele Telethon Institute for Gene Therapy to advance several gene therapy programs, including one for ß-thalassemia; Memorial Sloan Kettering, which received clearance for its IND from the FDA in 2012 for a Phase I/II gene therapy study; and Sangamo BioSciences Inc. (through its partnership with Biogen Idec), which has announced plans to initiate a Phase I clinical study using zinc finger nuclease-mediated gene-editing techniques in hemoglobinopathies including ß-thalassemia, Acceleron Pharma, Inc., which is investigating Luspatercept (ACE-536), a subcutaneously-delivered protein therapeutic that targets molecules in the TGF- superfamily, in a Phase III clinical trial in subjects with ß-thalassemia.

· Sickle cell disease: The current standard of care for the treatment of SCD in the developed world is chronic blood transfusions or hydroxyurea (a generic drug). In addition, such patients often receive iron chelation therapy to help manage the iron overload associated with chronic blood transfusions. We are aware of ongoing studies that continue to evaluate the efficacy and safety of hydroxyurea in various populations. In addition, some patients with SCD receive allogeneic HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. We understand that various biopharmaceutical companies and

academic centers around the world are seeking to develop improvements to allogeneic HSCT, including BPX-501, a modified donor T cell therapy in an ongoing Phase I/II study being supported by Bellicum Pharmaceuticals, Inc. A number of different therapeutic approaches are under investigation targeting the various aspects of SCD pathophysiology, including: pan-selectin inhibitors, including GMI-1070 in Phase II studies supported by GlycoMimetics Inc. (in 2011, Pfizer Inc. and GlycoMimetics Inc. entered a global collaboration to advance this compound); hemoglobin modifiers to prevent the sickling of RBC, including GBT440 in a Phase I/II study supported by Global Blood Therapeutics, Inc.; and also gene editing approaches being supported by Intellia Therapeutics, Inc. (in collaboration with Novartis AG), Editas Medicine, Inc. and CRISPR Therapeutics, Inc. (in collaboration with Vertex Pharmaceuticals Incorporated). There are also several different groups developing gene therapy approaches for SCD. Some of these groups use a similar ex vivo autologous approach, but make use of different vectors and different cell processing techniques. These include: UCLA, which has received funding from the California Institute of Regenerative Medicine to pursue a Phase I gene therapy study for SCD; and Cincinnati Children's Hospital Medical Center, which is conducting a Phase I/II gene therapy study for SCD and Sangamo BioSciences Inc. (through its partnership with Biogen Idec) which has announced plans to investigate the use of zinc finger nuclease-mediated gene-editing techniques in hemoglobinopathies including SCD, although to our knowledge no clinical studies have been initiated.

- CALD: The current standard of care for the treatment of CALD is allogeneic HSCT. We understand that various academic centers around the world are seeking to develop improvements to allogeneic HSCT. In addition, some physicians recommend glyceryl trierucate—better known as Lorenzo's Oil—to patients diagnosed with ALD or AMN. However, Lorenzo's Oil has not been clinically proven to address the cerebral symptoms of ALD, and has not been approved by any major regulatory agency as a prescription drug. There are efforts underway to obtain FDA approval for Lorenzo's Oil as a prescription drug.
- T cell-based immunotherapies for oncology: A number of pharmaceutical companies and academic collaborators are researching and developing T cell-based immunotherapies for oncology, including Novartis AG (in collaboration with the University of Pennsylvania), Adaptimmune Inc., Juno Therapeutics, Inc. (in collaboration with Celgene, Memorial Sloan Kettering and the Fred Hutchinson Cancer Research Center), Kite Pharma, Inc. (in collaboration with Amgen, Inc. and the National Institutes of Health), Pfizer Inc. (through their collaboration with Cellectis SA and Servier), among others. Many of the T cell-based immunotherapy programs being developed by these companies are already in Phase I/II clinical trials for multiple indications.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. Accordingly, our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, or more effectively marketed and sold, than any treatment we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our treatments.

These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical study sites and patient registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. We expect any treatments that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

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. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over competitive generic products.

Government regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. FDA approval must be obtained before clinical testing of biological products, and each clinical study protocol for a gene therapy product is reviewed by the FDA and, in some instances, the NIH, through its RAC. FDA

approval also must be obtained before marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the CBER regulates gene therapy products. The CBER works closely with the NIH and its 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. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in gene therapy INDs.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. biological products development process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical studies may begin;
- performance of adequate and well-controlled human clinical studies according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a Biologics License Application, or BLA, for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with GMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or GTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

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

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation is submitted to

and the study is registered with the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, however many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee that discusses 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.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve

any outstanding concerns before the clinical study can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

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

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

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

Post-approval clinical studies, sometimes referred to as Phase IV clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA 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 ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information

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

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

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

U.S. review and approval processes

After the completion of clinical studies of a biological product, FDA approval of a BLA, must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological 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. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

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

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the GTPs. These are 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 GTP 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. Additionally,

before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure GMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

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

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a risk management plan, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical studies, sometimes referred to as Phase IV clinical studies, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

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

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA or BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited development and review programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is

acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Under the Breakthrough Therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint

other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, Breakthrough Therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Post-approval requirements

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

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

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products 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 GMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain GMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, 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. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

Additional regulation

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

U.S. Foreign Corrupt Practices Act

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

Government regulation outside of the United States

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

countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the European Union, for example, a CTA must be submitted for each clinical trial to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the corresponding clinical study may proceed.

The requirements and process governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The European Union also provides opportunities

for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

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

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

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

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

The EMA has established the Adaptive Pathways program intended to expedite or facilitate either an initial approval of a drug in a well-defined patient subgroup with a high medical need and subsequent widening of the indication to a larger patient population, or an early regulatory approval (e.g., conditional approval), which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on a drug's use in patients. The approach builds in regulatory processes already in place within the existing EU legal framework.

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

Employees

As of January 31, 2016, we had 254 full-time employees, 70 of whom have Ph.D., M.D. or Pharm.D. degrees. Of these full-time employees, 199 employees are engaged in research and development activities and 55 employees are engaged in finance, legal, business development, human resources, information technology, facilities and other general administrative functions. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relations with our employees to be good.

Corporate Information

We were incorporated in Delaware in April 1992 under the name Genetix Pharmaceuticals, Inc., and subsequently changed our name to bluebird bio, Inc. in September 2010. Our mailing address and executive offices are located at 150 Second Street, Third

Floor, Cambridge, Massachusetts and our telephone number at that address is (339) 499-9300. We maintain an Internet website at the following address: www.bluebirdbio.com. The information on our website is not incorporated by reference in this annual report on Form 10-K or in any other filings we make with the Securities and Exchange Commission, or SEC.

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended. These include our annual reports on Form 10-K, our quarterly reports on Form 10-Q, and our current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

Item 1A. Risk Factors

An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our financial statements and related notes hereto, before deciding to invest in our common stock. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

Risks related to the discovery and development of our product candidates

Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval. At the moment, no gene therapy products have been approved in the United States and only one product has been approved in the European Union, or EU.

We have concentrated our therapeutic product research and development efforts on our gene therapy platform, and our future success depends on the successful development of this therapeutic approach. There can be no assurance that any development problems we experience in the future related to our gene therapy platform will not cause significant delays or unanticipated costs, or that such development problems can be solved. We may also experience delays in developing a sustainable, reproducible and commercial-scale manufacturing process or transferring that process to commercial partners, which may prevent us from completing our clinical studies or commercializing our products on a timely or profitable basis, if at all.

In addition, the clinical study requirements of the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA and other regulatory agencies 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 potential products. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied pharmaceutical or other product candidates. At the moment, only one gene therapy product, UniQure’s Glybera, which received marketing authorization in the EU in 2012, has been approved in the Western world, which makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, the EU or other jurisdictions. Approvals by the EMA and the European Commission may not be indicative of what the FDA may require for approval.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. For example, the FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical studies conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health, or NIH, are also subject to review by the NIH Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or RAC. Although the FDA decides whether individual gene therapy protocols may proceed, the RAC review process can impede the initiation of a clinical study, even if the FDA has reviewed the study and approved its initiation. For example, although we have discussed with the FDA the protocol design for a Phase III clinical study in pediatric subjects for our LentiGlobin product candidate, the RAC completed its public review in June 2015 and recommended a delay of initiation of a Phase III pediatric clinical study in the United States for an additional one to two years. We cannot predict if this recommendation may delay enrollment of such a pediatric clinical study. Clinical trial sites in the United States that receive NIH funding for research involving recombinant or synthetic nucleic acid molecules are required to follow RAC recommendations, or risk losing NIH funding for such research or needing NIH pre-approval before conducting such research. In addition, the FDA can put an investigational new drug application, or IND, on clinical hold if the information in an IND is not sufficient to assess the risks in pediatric patients. Before a clinical study can begin at any institution, that institution's institutional review board, or IRB, and its Institutional Biosafety Committee will have to review the proposed clinical study to assess the safety of the study. Moreover, serious adverse events or developments in clinical trials of gene therapy product candidates conducted by others may cause the FDA or other regulatory bodies to initiate a clinical hold on our clinical trials or otherwise change the requirements for approval of any of our product candidates.

These regulatory review agencies, committees and advisory groups and the new requirements and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional or larger studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval studies, limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

We may find it difficult to enroll patients in our clinical studies, which could delay or prevent clinical studies of our product candidates.

Identifying and qualifying patients to participate in clinical studies of our product candidates is critical to our success. The timing of our clinical studies depends on the speed at which we can recruit eligible patients to participate in testing our product candidates. We have experienced delays in some of our clinical studies, and we may experience similar delays in the future. If patients are unwilling to participate in our gene therapy studies because of negative publicity from adverse events in the biotechnology or gene therapy industries or for other reasons, including competitive clinical studies for similar patient populations, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical studies altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a study, to complete our clinical studies in a timely manner. Patient enrollment is affected by factors including:

- severity of the disease under investigation;
- design of the study protocol;
- size of the patient population;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study, including as a result of adverse effects observed in similar or competing therapies;
- proximity and availability of clinical study sites for prospective patients;
- availability of competing therapies and clinical studies;
- efforts to facilitate timely enrollment in clinical studies;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

In particular, each of the conditions for which we plan to evaluate our current hematopoietic stem cell, or HSC, product candidates are rare genetic disorders with limited patient pools from which to draw for clinical studies. It has been estimated that about 1.5% (80 to 90 million people) of the global population are carriers of ß-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. According to Thalassemia International Federation, about 288,000 patients with transfusion-dependent -thalassemia, or TDT, are alive and registered as receiving regular treatment around the world, of which we estimate that about 10,000-15,000 live in the United States and Europe. The global incidence of SCD is estimated to be 250,000-300,000 births annually with a global prevalence estimated to be about 20-25 million. The worldwide incidence rate for adrenoleukodystrophy, the superset of cerebral adrenoleukodystrophy, or CALD, is approximately one in 17,000 newborns. CALD in young boys accounts for about 30-40% of patients diagnosed with adrenoleukodystrophy. Further, because newborn screening for CALD is not widely adopted, and it can be difficult to diagnose CALD in the absence of a genetic screen, we may have difficulty finding patients who are eligible to participate in our study. The eligibility criteria of our clinical studies will further limit the pool of available study participants. Additionally, the

process of finding and diagnosing patients may prove costly. Finally, our treatment process requires that the procurement of autologous cells from subjects be conducted where the cells can be shipped to a transduction facility within the required timelines, as the HSCs and T cells, in the case of our oncology product candidate, have limited viability following harvest.

Our current product candidates are being developed to treat rare conditions and certain cancers. We plan to seek initial marketing approval in the United States and the European Union. We may not be able to initiate or continue clinical studies if we cannot enroll a sufficient number of eligible patients to participate in the clinical studies required by the FDA or the EMA or other regulatory agencies. Our ability to successfully initiate, enroll and complete a clinical study in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical studies;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical studies as planned, we may need to delay, limit or terminate ongoing or planned clinical studies, any of which would have an adverse effect on our business.

We may encounter substantial delays in our clinical studies or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety, purity and potency, or efficacy, of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory agencies on study design;
- delays in obtaining required IRB or Institutional Ethics Committee approval at each clinical study site;
- delays in recruiting suitable patients to participate in our clinical studies;
- imposition of a clinical hold by regulatory agencies, after an inspection of our clinical study operations or study sites or due to unforeseen safety issues;
- failure by our CROs, other third parties or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA’s good clinical practices, or GCP, or applicable regulatory requirements in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- failure to obtain sufficient cells from patients to manufacture enough drug product or achieve target cell doses;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical study sites or patients dropping out of a study;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to demonstrate comparability of our modified product candidates to earlier versions. Clinical study delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

If the results of our clinical studies are inconclusive or if there are safety concerns or adverse events associated with our product candidates, we may:

- be delayed in obtaining regulatory approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;

- be required to perform additional clinical studies or clinical studies of longer duration to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its use;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Treatment with our gene therapy product candidates involves chemotherapy and myeloablative treatments, which can cause side effects or adverse events that are unrelated to our product candidates, but may still impact the success of our clinical studies. Additionally, our product candidates could potentially cause other adverse events that have not yet been predicted. The inclusion of critically ill patients in our clinical studies may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using, or the progression of their disease. As described above, any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products.

We have not completed any clinical studies of our current viral vectors or product candidates derived from these viral vectors. Initial success in our ongoing clinical studies may not be indicative of results obtained when these studies are completed. Furthermore, success in early clinical studies may not be indicative of results obtained in later studies.

Our current viral vectors and our product candidates first initiated evaluation in human clinical studies in 2013, and we may experience unexpected results in the future. Earlier gene therapy clinical studies, which we believe serve as proof-of-concept for our product candidates, utilized lentiviral vectors similar to ours. However, these studies should not be relied upon as evidence that our ongoing or future clinical studies will succeed. Study designs and results from previous studies are not necessarily predictive of our future clinical study designs or results, and initial results may not be confirmed upon full analysis of the complete study data. There is limited data concerning long-term safety and efficacy following treatment with our gene therapy product candidates. These data, or other positive data, may not continue or occur for these subjects or for any future subjects in our ongoing or future clinical studies, and may not be repeated or observed in ongoing or future studies involving our product candidates. For instance, while patients with TDT or severe SCD who have been treated with our LentiGlobin product candidate may experience a reduction or temporary elimination of transfusion support, there can be no assurance that they will not require transfusion support in the future. Furthermore, our product candidates may also fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical studies. There can be no assurance that any of these studies will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates.

There is a high failure rate for drugs and biologics proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical studies even after achieving promising results in earlier stage clinical studies. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, regulatory delays or rejections may be encountered as a result of many factors, including changes in regulatory policy during the period of product development.

Patients with different genotypes may respond differently to treatment with our product candidates, which may result in the delay of our clinical development and commercialization plans.

Initial results from our ongoing clinical studies suggest that patients with TDT who do not have the $^{0}/^{0}$ genotype respond better to treatment with our LentiGlobin product candidate than patients who do have the $^{0}/^{0}$ genotype. Consequently, we expect to seek FDA approval of our LentiGlobin product candidate initially for the treatment of TDT in patients who do not have the $^{0}/^{0}$ genotype. These differences in responsiveness require us to engage regulatory authorities in additional discussions. In order to support an application for FDA approval of our LentiGlobin product candidate in patients who have the $^{0}/^{0}$ genotype, we will need to conduct additional clinical studies, but we do not yet have plans regarding when these trials will commence, or when our LentiGlobin product candidate may be

commercially available to all genotypes.

The results from our Starbeam Study may not be sufficiently robust to support the submission of marketing approval for our Lenti-D product candidate. Before we submit our Lenti-D product candidate for marketing approval, the FDA and the EMA may require us to enroll additional subjects, conduct additional clinical studies, or evaluate subjects for an additional follow-up period.

The FDA has advised us that our Starbeam Study, which is a single-arm, open-label study to evaluate the safety and efficacy of our Lenti-D product candidate to halt the progression of CALD, may not be deemed to be a pivotal study or may not provide sufficient support for a Biologics License Application, or BLA, submission. The FDA normally requires two pivotal clinical studies to approve a drug or biologic product, and thus the FDA may require that we conduct larger or additional clinical studies of our Lenti-D product candidate prior to a BLA submission. The FDA typically does not consider a single clinical study to be adequate to serve as a pivotal

study unless it is, among other things, well-controlled and demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, and a confirmatory study would be practically or ethically impossible. Due to the nature of CALD and the limited number of patients with this condition, we believe a placebo-controlled and blinded study is not practicable for ethical and other reasons. However, it is still possible that, even if we achieve favorable results in the Starbeam Study, the FDA may require us to enroll additional subjects or conduct additional clinical studies, possibly involving a larger sample size or a different clinical study design, particularly if the FDA does not find the results from the Starbeam Study to be sufficiently persuasive to support a BLA submission. The FDA may also require that we conduct a longer follow-up period of subjects treated with our Lenti-D product candidate prior to accepting our BLA submission.

In addition, the Starbeam Study was not designed to achieve a statistically significant efficacy determination. Rather, we anticipate that the safety and efficacy of our Lenti-D product candidate will be evaluated in light of the data collected in our retrospective ALD-101 Study and our observational ALD-103 study. However, due to the retrospective nature of the ALD-101 study, and the limited number of patients with this condition, the FDA has advised us that the ALD-101 Study is not sufficiently robust to serve as a conventional historical control group and as a basis of comparison against the results of the Starbeam Study. Thus, we expect that the FDA will assess the totality of the safety and efficacy data from our CALD clinical studies in reviewing any future BLA submission for our Lenti-D product candidate. Based on this assessment, the FDA may require that we conduct additional preclinical or clinical studies prior to submitting or approving a BLA for this indication.

It is possible that the FDA or the EMA may not consider the results of this study to be sufficient for approval of our Lenti-D product candidate for this indication. If the FDA or the EMA requires additional studies, we would incur increased costs and delays in the marketing approval process, which may require us to expend more resources than we have available. In addition, it is possible that the FDA and the EMA may have divergent opinions on the elements necessary for a successful BLA and Marketing Authorization Application, or MAA, respectively, which may cause us to alter our development, regulatory and/or commercialization strategies.

We cannot be certain that our planned Phase III clinical studies of our LentiGlobin product candidate, together with data from our ongoing TDT clinical studies (Northstar and HGB-205), will be sufficient to form the basis for a BLA submission for our LentiGlobin product candidate.

In general, the FDA requires the successful completion of two pivotal trials to support approval of a BLA, but in certain circumstances, will approve a BLA based on only one pivotal trial. If successful, we believe the results from our planned Phase III clinical studies in patients with TDT who do not have the $^{0}/_{0}$ genotype, together with data from our ongoing TDT clinical studies (Northstar and HGB-205), could be sufficient to form the basis for a BLA submission for our LentiGlobin product candidate to treat patients with TDT who do not have the $^{0}/_{0}$ genotype. However, it should be noted that our ability to submit and obtain approval of a BLA is ultimately an FDA review decision, which will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support the submission or approval of a BLA. Depending on the outcome of these planned and ongoing clinical studies, the FDA may require that we conduct additional or larger pivotal trials before we can submit or obtain approval for a BLA for our LentiGlobin product candidate for the treatment of TDT.

In June 2015, the RAC recommended that we delay the initiation of a Phase III clinical study for pediatric patients with TDT for one to two years. Any delay in the initiation or completion of such a study could similarly delay our ability to submit a BLA for our LentiGlobin product candidate or obtain full approval in Europe.

Before beginning our planned Phase III clinical studies of our LentiGlobin product candidate, the FDA must review the final protocols for the studies, along with additional information supporting the respective proposed study designs. Concurrent with starting the studies, the FDA will review certain updated chemistry, manufacturing and controls, or CMC, information that we are required to submit. If the FDA does not approve the protocols for the planned studies in

the forms in which we submit them, or if the FDA is not satisfied with the additional CMC information we plan to provide, the start or continuation of these clinical studies may be delayed or the design of the studies may change.

There can be no assurance that we will ultimately receive conditional marketing approval of our LentiGlobin product candidate in the European Union, or the nature of the conditions that would be imposed on us if conditionally approved.

The EMA Adaptive Pathways program in which we are participating is intended to facilitate either an initial approval in a well-defined patient subgroup with a high medical need and subsequent widening of the indication to a larger patient population, or an early regulatory approval (e.g. conditional approval), which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on a drug's use in patients. Based on our discussions with the EMA, we believe our LentiGlobin product candidate may be eligible for conditional approval under this program for the treatment of patients with TDT on the basis of the totality of clinical data, in particular reduction in transfusion need, from the ongoing Northstar study and supportive HGB-205 study.

However, it should be noted that the EMA Adaptive Pathways program is a pilot program, and as such there is limited information and precedent regarding the potential outcomes for sponsors that participate in this program. Whether our LentiGlobin product candidate is eligible for conditional approval will ultimately be determined at the discretion of the EMA and will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support conditional approval. Depending on the outcome of our planned and ongoing clinical trials, the EMA may require that we conduct additional or larger clinical trials before our LentiGlobin product candidate is eligible for conditional approval. Even if conditional approval is obtained, the conditions to be imposed on us under this program are unknown and will be imposed at the time of any such conditional approval.

Changes in our manufacturing processes may cause delays in our clinical development and commercialization plans.

The manufacturing processes for our lentiviral vectors and our product candidates are complex. As we develop a commercial-scale manufacturing process for our LentiGlobin and Lenti-D product candidates, we are exploring improvements to the manufacturing process for both producing our lentiviral vectors and for our product candidates on a continual basis. In some circumstances, changes in the manufacturing process may require us to perform additional comparability studies or to collect additional data from patients prior to undertaking additional clinical studies. The FDA may also require us to file a new IND with respect to such changes in our manufacturing process. These requirements may lead to delays in our clinical development and commercialization plans.

In previous clinical studies involving viral vectors for gene therapy, some subjects experienced serious adverse events, including the development of leukemia due to vector-related insertional oncogenesis. If our vectors demonstrate a similar effect, we may be required to halt or delay further clinical development of our product candidates.

A significant risk in any gene therapy product based on viral vectors is that the vector will insert in or near cancer-causing oncogenes leading to uncontrolled clonal proliferation of mature cancer cells in the patient. For example, in 2003, 20 subjects treated for X-linked severe combined immunodeficiency in two gene therapy studies using a murine, or mouse-derived, gamma-retroviral vector showed correction of the disease, but the studies were terminated after five subjects developed leukemia (four of whom were subsequently cured). The cause of these adverse events was shown to be insertional oncogenesis, which is the process whereby the corrected gene inserts in or near a gene that is important in a critical cellular process like growth or division, and this insertion results in the development of a cancer (often leukemia). Using molecular diagnostic techniques, it was determined that clones from these subjects showed retrovirus insertion in proximity to the promoter of the LMO2 proto-oncogene. Earlier generation retroviruses like the one used in these two studies have been shown to preferentially integrate in regulatory regions of genes that control cell growth.

These well-publicized adverse events led to the development of new viral vectors, such as lentiviral vectors, with improved safety profiles and also the requirement of enhanced safety monitoring in gene therapy clinical trials, including periodic analyses of the therapy's genetic insertion sites. In published studies, lentiviral vectors have demonstrated an improved safety profile over gamma-retroviral vectors, with no disclosed events of gene therapy-related adverse events, which we believe is due to a number of factors including the tendency of these vectors to integrate within genes rather than in areas that control gene expression, as well as their lack of strong viral enhancers. However, it should be noted that in our Phase I/II study (the LG001 Study) of autologous HSCs transduced ex vivo using an earlier generation of our LentiGlobin vector, called HPV569, we initially observed in one subject that a disproportionate number of the cells expressing our functional gene had the same insertion site. Tests showed that this partial clonal dominance contained an insertion of the functional gene in the HMGA2 gene that persisted for a period of two to three years. Although there was some initial concern that the observed clonal dominance might represent a pre-leukemic event, there have been no adverse clinical consequences of this event, or any signs of cancer, in over seven years since the observation was made. The presence of the HMGA2 clone has steadily declined in this subject over time to the point that it is no longer the most common clone observed in this subject.

Notwithstanding the historical data regarding the potential safety improvements of lentiviral vectors, the risk of insertional oncogenesis remains a significant concern for gene therapy and we cannot assure that it will not occur in any of our ongoing or planned clinical studies. There is also the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. The FDA has stated that lentiviral vectors possess characteristics that may pose high risks of delayed adverse events. If any such adverse events occur, further advancement of our clinical studies could be halted or delayed, which would have a material adverse effect on our business and operations.

In previous clinical studies involving T cell-based immunotherapies, some subjects experienced serious adverse events. Our T cell-based immunotherapy product candidates may demonstrate a similar effect or have other properties that could halt their clinical development, prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences.

Our bb2121 product candidate is a chimeric antigen receptor, or CAR, T cell-based immunotherapy. In previous clinical studies involving CAR T cell product candidates from other companies or academic researchers, some subjects experienced serious adverse events, including febrile neutropenia, chemical laboratory abnormalities, low blood counts, neurotoxicity, and significant, acute

toxicities with symptoms thought to be associated with the release of cytokines. These symptoms included fever, low blood pressure and kidney dysfunction. Some patients also experienced toxicity of the central nervous system, such as confusion, somnolence and speech impairment. There have been life threatening events related to cytokine release syndrome and toxicities of the central nervous system. Some of these events required intense medical intervention such as intubation. Several patients have died in clinical trials of these CAR T cell product candidates.

Undesirable side effects caused by our bb2121 product candidate, or our other T cell-based immunotherapy product candidates, could cause us or regulatory authorities to interrupt, delay or halt clinical studies and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign regulatory authorities. Results of our studies could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Treatment-related side effects could also affect patient recruitment or the ability of enrolled subjects to complete the studies or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from T cell-based immunotherapies are not normally encountered in the general patient population and by medical personnel. We expect to have to train medical personnel regarding our T cell-based immunotherapy product candidates to understand their side effects for both our planned clinical trials and upon any commercialization of any T cell-based immunotherapy product candidates. Inadequate training in recognizing or managing the potential side effects of T cell-based immunotherapy product candidates could result in patient deaths. Any of these occurrences may harm our business, financial condition and prospects significantly.

Even if we complete the necessary preclinical and clinical studies, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate or the approval may be for a more narrow indication than we expect.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical studies, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory advisory group or authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical studies and the review process. Regulatory agencies also may approve a treatment candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our treatment candidates. For example, the development of our product candidates for pediatric use is an important part of our current business strategy, and if we are unable to obtain regulatory approval for the desired age ranges, our business may suffer.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory scrutiny.

Even if we obtain regulatory approval in a jurisdiction, the regulatory authority may still impose significant restrictions on the indicated uses or marketing of our product candidates, or impose ongoing requirements for potentially costly post-approval studies, post-market surveillance or patient or drug restrictions. For example, the FDA typically advises that patients treated with gene therapy undergo follow-up observations for potential adverse events for a 15-year period. Additionally, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with good manufacturing practices,

or GMP, and adherence to commitments made in the BLA. If we or a regulatory agency discovers previously unknown problems with a product such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical studies;
- refuse to approve a pending marketing application, such as a BLA or supplements to a BLA submitted by us;

- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

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 inhibit our ability to commercialize our product candidates and generate revenues.

Risks related to our reliance on third parties

We expect to rely on third parties to conduct some or all aspects of our vector production, drug product manufacturing, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our vector production, product manufacturing, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to these items. In some cases these third parties are academic, research or similar institutions that may not apply the same quality control protocols utilized in certain commercial settings.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND-enabling studies and clinical studies are conducted in accordance with the study plan and protocols.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the preclinical and clinical studies required to support future IND and BLA submissions and approval of our product candidates.

Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;
- the risk that these activities are not conducted in accordance with our study plans and protocols;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

Any of these events could lead to clinical study delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and product candidates. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain and we may be unable to transfer or sublicense the intellectual property

rights we may have with respect to such activities.

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Some components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with GMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary

documentation in support of a BLA or MAA on a timely basis and where required, must adhere to the FDA's or other regulator's good laboratory practices, or GLP, and GMP regulations enforced by the FDA or other regulator through facilities inspection programs. Some of our contract manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA or other regulatory approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA or other regulatory approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other regulators can impose regulatory sanctions including, among other things, refusal to approve a pending application for a biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. The number of manufacturers with the necessary manufacturing capabilities is limited. In addition, an alternative manufacturer would need to be qualified through a BLA supplement or similar regulatory submission which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical studies, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed or we could lose potential revenue.

We expect to rely on third parties to conduct, supervise and monitor our clinical studies, and if these third parties perform in an unsatisfactory manner, it may harm our business.

We expect to rely on CROs and clinical study sites to ensure our clinical studies are conducted properly and on time. While we will have agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our clinical studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA's GCPs for conducting, recording and reporting the results of clinical studies to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical study participants are protected. The FDA enforces these GCPs through periodic inspections of study sponsors, principal investigators and clinical study sites. If we or our CROs fail to comply with applicable

GCPs, the clinical data generated in our future clinical studies may be deemed unreliable and the FDA may require us to perform additional clinical studies before approving any marketing applications. Upon inspection, the FDA may determine that our clinical studies did not comply with GCPs. In addition, our future clinical studies will require a sufficient number of test subjects to evaluate the safety and efficacy of our product candidates. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical studies, which would delay the regulatory approval process.

Employees of our CROs are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs, which must be conducted in accordance with GCPs and GLPs, respectively. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical studies or other drug development activities that could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical studies may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

We also expect to rely on other third parties to store and distribute our vectors and products for any clinical studies that we may conduct. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, if approved, producing additional losses and depriving us of potential product revenue.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture our vectors and our product candidates, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy platform, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks related to our financial condition and capital requirements

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a clinical-stage biotechnology company, and we have not yet generated significant revenues. We have incurred net losses in each year since our inception in 1992, including net losses of $166.8 million and $48.7 million for the years ended December 31, 2015 and 2014, respectively. As of December 31, 2015, we had an accumulated deficit of $314.2 million.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. To date, we have financed our operations primarily through the sale of equity securities and, to a lesser extent, through collaboration agreements and grants from governmental agencies and charitable foundations. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings, strategic collaborations or additional grants. We have not completed pivotal clinical studies for any product candidate and it will be several years, if ever, before we have a product candidate ready for commercialization. Even if we obtain regulatory approval to market a product candidate, our future revenues will depend upon the size of any markets in which our product candidates have received approval, and our ability to

achieve sufficient market acceptance, reimbursement from third-party payors and adequate market share for our product candidates in those markets.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our research and preclinical and clinical development of our product candidates;
- expand the scope of our current clinical studies for our product candidates;
- initiate additional preclinical, clinical or other studies for our oncology product candidates;
- further develop the manufacturing process for our vectors or our product candidates;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;

- seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- make milestone or other payments under any license agreements or our stock purchase agreement with the former equityholders of Pregenen;
- maintain, protect and expand our intellectual property portfolio;
- establish a sales, marketing and distribution infrastructure in the United States and Europe to commercialize any products for which we may obtain marketing approval;
- attract and retain skilled personnel;
- build additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

We have never generated any revenue from product sales and may never be profitable.

Our ability to generate revenue and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory, pricing and reimbursement approvals necessary to commercialize our product candidates. We do not anticipate generating revenues from product sales for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing research and preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- developing a sustainable, commercial-scale, reproducible, and transferable manufacturing process for our vectors and product candidates;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for our product candidates, if approved;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval, either by collaborating with a partner or, if launched independently, by establishing a sales force, marketing and distribution infrastructure;
- obtaining sufficient pricing and reimbursement for our product candidates from third-party and governmental payors;
- obtaining market acceptance of our product candidates and gene therapy as a viable treatment option;
- addressing any competing technological and market developments;
- identifying and validating new gene therapy product candidates;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter; and
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the U.S. Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory agencies, domestic or foreign, to perform clinical and other studies in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

From time to time, we will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We are currently advancing our LentiGlobin, Lenti-D and bb2121 product candidates through clinical development and other product candidates through preclinical development. Developing gene therapy products is expensive, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance our product candidates in clinical studies.

As of December 31, 2015, our cash, cash equivalents and marketable securities were $865.8 million. We expect that our existing cash, cash equivalents, and marketable securities will be sufficient to fund our current operations through 2018. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic objectives.

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. In addition, 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 stockholders 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 stockholders. 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 collaborative partners 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 candidates 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.

Risks related to commercialization of our product candidates

We intend to rely on third-party manufacturers to produce our vector, product candidates and other key materials, but we have not entered into binding agreements with any such manufacturers to support commercialization. Additionally, these manufacturers do not have experience producing our vectors and product candidates at commercial levels and may not achieve the necessary regulatory approvals or produce our vectors and products at the quality, quantities, locations and timing needed to support commercialization.

We have not yet secured manufacturing capabilities for commercial quantities of our viral vectors or established transduction facilities in all of the desired commercialization regions to support commercialization of our products. Although we intend to rely on third-party manufacturers for commercialization, we have only entered into agreements with such manufacturers to support our clinical studies. We may be unable to negotiate binding agreements with the manufacturers to support our commercialization activities at commercially reasonable terms.

No manufacturer currently has the experience or ability to produce our vectors and product candidates at commercial levels. We are currently developing a commercial-scale manufacturing process for our LentiGlobin and Lenti-D product candidates, which we are transferring to one or more contract manufacturers. We may run into technical or scientific issues related to manufacturing or development that we may be unable to resolve in a timely manner or with available funds. Although we have been able to produce our Lenti-D vector at commercial scale, we have not completed the characterization and validation activities necessary for commercial and regulatory approvals. If our manufacturing partners do not obtain such regulatory approvals, our commercialization efforts will be harmed.

Additionally, since the HSCs and T cells have a limited window of stability following procurement from the subject, we must set up transduction facilities in the regions where we wish to commercialize our product. Currently, we rely on third-party contract manufacturers in the United States and Europe to produce our product candidates for our clinical studies. Since a portion of our target patient populations will be outside the United States and Europe, we will need to set up additional transduction facilities that can replicate our transduction process. Establishment of such facilities may be financially impractical or impeded by technical, quality, or

regulatory issues related to these new sites and we may also run into technical or scientific issues related to transfer of our transduction process or other developmental issues that we may be unable to resolve in a timely manner or with available funds.

Even if we timely develop a manufacturing process and successfully transfer it to the third-party vector and product manufacturers, if such third-party manufacturers are unable to produce the necessary quantities of viral vectors and our product candidates, or in compliance with GMP or other pertinent regulatory requirements, and within our planned time frame and cost parameters, the development and sales of our products, if approved, may be materially harmed.

In addition, any significant disruption in our supplier relationships could harm our business. We source key materials from third parties, either directly through agreements with suppliers or indirectly through our manufacturers who have agreements with suppliers. There are a small number of suppliers for certain key materials that are used to manufacture our product candidates. Such suppliers may not sell these key materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these key materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these key materials.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenues.

We have no experience selling and marketing our product candidates. To successfully commercialize any products that may result from our development programs, we will need to develop these capabilities in the United States, Europe and other regions, either on our own or with others. We may enter into collaborations with other entities to utilize their mature marketing and distribution capabilities, but we may be unable to enter into marketing agreements on favorable terms, if at all. If our future collaborative partners do not commit sufficient resources to commercialize our future products, if any, and we are unable to develop the necessary marketing capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without a significant internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates.

We are engaged in gene therapy for severe genetic and rare diseases and in the field of T cell-based immunotherapy, both of which are competitive and rapidly changing fields. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Some of the pharmaceutical and biotechnology companies we expect to compete with include GlaxoSmithKline plc through their collaboration with TIGET/MolMed, Sangamo BioSciences Inc. through their collaboration with Biogen Idec, Bellicum Pharmaceuticals, Inc., Global Blood Therapeutics, Inc., Novartis AG through their collaboration with the University of Pennsylvania, GlycoMimetics Inc., Acceleron Pharma, Inc., Kite Pharma, Inc., Pfizer Inc. through their collaboration with Cellectis SA, Adaptimmune Inc. and Juno Therapeutics, Inc. through their collaboration with Celgene Corporation. In addition, many universities and private and public research institutes are active in our target disease areas.

Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, manufacturing capabilities, experienced marketing and manufacturing organizations. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or

licensing on an exclusive basis, products that are more effective or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization and market penetration than us. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars due to the changing regulatory environment. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. This pathway could allow competitors to reference data from biological products already approved after 12 years from the time of approval. In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data from biological products already approved, but will not be able to get on the market until 10 years after the time of approval. This 10-year period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products. If competitors are able to obtain marketing

approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences. Expiration or successful challenge of our applicable patent rights could also trigger competition from other products, assuming any relevant exclusivity period has expired.

In addition, although our product candidates have been granted orphan drug status by the FDA and EMA, there are limitations to the exclusivity. In the United States, the exclusivity period for orphan drugs is seven years, while pediatric exclusivity adds six months to any existing patents or exclusivity periods. In Europe, orphan drugs may be able to obtain 10 years of marketing exclusivity and up to an additional two years on the basis of qualifying pediatric studies. However, orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria. Additionally, a marketing authorization holder may lose its orphan exclusivity if it consents to a second orphan drug application or cannot supply enough drug. Orphan drug exclusivity also can be lost when a second applicant demonstrates its drug is "clinically superior" to the original orphan drug.

Finally, 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. 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.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Ethical, social and legal concerns about gene therapy and genetic research could result in additional regulations restricting or prohibiting the products and processes we may use. Even with the requisite approvals, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party or governmental payors accepting gene therapy products in general, and our product candidates in particular, as medically useful, cost-effective, and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects resulting from the chemotherapy and myeloablative treatments associated with the procedure by which our product candidates are administered;
- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- the pricing of our products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical and clinical studies, market acceptance of the product will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of the product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors.

If we obtain approval to commercialize our product candidates outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

If any of our product candidates are approved for commercialization, we may enter into agreements with third parties to market them on a worldwide basis or in more limited geographical regions. We expect that we will be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights;

- economic weakness, including inflation, or political instability in particular foreign economies and markets; and
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.

The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments, such as stem cell transplants or gene therapy. In addition, because our CAR and TCR T cell product candidates represent new approaches to the treatment of cancer, we cannot accurately estimate the potential revenue. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products, including gene therapies. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries. In addition, costs or difficulties associated with the reimbursement of Glybera could create an adverse environment for reimbursement of other gene therapies.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries has and will continue to put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medicines, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Moreover, increasing efforts by governmental and third-party payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the Health Care Reform Law, was passed, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Health Care Reform Law, among other things, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and promoted a new Medicare Part D coverage gap discount program.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year. On

January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, delayed for another two months the budget cuts mandated by these sequestration provisions of the Budget Control Act of 2011. On March 1, 2013, the President signed an executive order implementing sequestration, and on April 1, 2013, the 2% Medicare payment reductions went into effect. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures. For each state that does not choose to expand its Medicaid program, there may be fewer insured patients overall, which could impact the sales, business and financial condition of manufacturers of branded prescription drugs or other therapies. Where patients receive insurance coverage under any of the new options made available through the Affordable Care Act, the possibility exists that manufacturers may be required to pay Medicaid rebates on that resulting drug utilization, a decision that could impact manufacturer revenues. The U.S. federal government also has announced delays in the implementation of key provisions of the Affordable Care Act. The implications of these delays for our and our partners' business and financial condition, if any, are not yet clear.

The delivery of healthcare in the European Union, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize any products for which we obtain marketing approval.

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

Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

Our target patient populations are relatively small, as a result, the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our products.

If the market opportunities for our product candidates are smaller than we believe they are, our revenues may be adversely affected and our business may suffer. Because the target patient populations of our product candidates are small, we must be able to successfully identify patients and achieve a significant market share to maintain profitability and growth.

We focus our research and product development on treatments for severe genetic and rare diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may change the estimated incidence or prevalence of these diseases. The number of patients in the United States, Europe and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products, or new patients may become increasingly difficult to identify or gain access

to, all of which would adversely affect our results of operations and our business.

The market opportunities for our T cell-based immunotherapy product candidates may be limited to those patients who are ineligible for or have failed prior treatments and may be small.

Our first clinical study of bb2121, our lead T cell-based immunotherapy product candidate, will be conducted with patients who have been diagnosed with relapsed/refractory multiple myeloma. The FDA often approves new therapies initially only for use in patients with relapsed or refractory advanced disease. We expect to initially seek approval of our T cell-based immunotherapy product candidates in this setting. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval in earlier lines of treatment and potentially as a first line therapy, but there is no guarantee that our product candidates, even if approved, would be approved for earlier lines of therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

Our projections of both the number of people who have the cancers we may be targeting, as well as the subset of people with these cancers in a position to receive second or third line therapy, and who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these cancers. The number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates. Even if we obtain significant market share for our product candidates, because the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

Risks related to our business operations

If we undertake business combinations, collaborations or similar strategic transactions, they may disrupt our business, divert management's attention, dilute stockholder value or be difficult to integrate.

On a regular basis, we consider various business combination transactions, collaborations, license agreements and strategic transactions with third parties, including transactions which may result in us acquiring, or being acquired by, a third party. The consummation or performance of any future business combination, collaboration or strategic transaction may involve risks, such as:

- diversion of managerial resources from day-to-day operations;
- challenges associated with integrating acquired technologies and operations of acquired companies;
- exposure to unforeseen liabilities;
- difficulties in the assimilation of different cultures and practices, as well as in the assimilation and retention of broad and geographically dispersed personnel and operations;
- misjudgment with respect to value, return on investment or strategic fit;
- higher than expected transaction costs; and
- additional dilution to our existing stockholders if we issue equity securities as consideration for any acquisitions.

As a result of these risks, we may not be able to achieve the expected benefits of any such transaction. If we are unsuccessful in completing or integrating any acquisition, we may be required to reevaluate that component of our strategy only after we have incurred substantial expenses and devoted significant management time and resources in seeking to complete and integrate the acquisition.

Future business combinations could involve the acquisition of significant intangible assets. We may need to record write-downs from future impairments of identified intangible assets and goodwill. These accounting charges would increase a reported loss or reduce any future reported earnings. In addition, we could use substantial portions of our available cash to pay the purchase price for company or product candidate acquisitions. Subject to the limitations under our existing indebtedness, it is possible that we could incur additional debt or issue additional equity securities as consideration for these acquisitions, which could cause our stockholders to suffer significant dilution.

The failure to successfully integrate Precision Genome Engineering, Inc.'s business and operations or fully realize the benefits of this acquisition may adversely affect our future results.

On June 30, 2014, we acquired all of the outstanding capital stock of Precision Genome Engineering, Inc., or Pregenen. Based in Seattle, Washington, Pregenen was focused on the development of gene editing and cell signaling technologies. The success of our acquisition of Pregenen depends, in part, on our ability to successfully integrate Pregenen's business and operations and fully realize the anticipated benefits and synergies from combining our business with Pregenen's business, in particular our ability to advance Pregenen's gene editing and cell signaling technologies to the stage where they can be incorporated into our existing or new product candidates. However, to realize these anticipated benefits, we must successfully combine these businesses and continue the research and

development activities previously undertaken by Pregenen as a stand-alone company. If we are unable to achieve these objectives, the anticipated benefits of our acquisition of Pregenen may not be realized fully or at all or may take longer to realize than expected. Any failure to timely realize these anticipated benefits could have a material adverse effect on our development programs, expenses and operating results.

Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments they are already familiar with and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, in 2003, 20 subjects treated for X-linked severe combined immunodeficiency in two gene therapy studies using a murine gamma-retroviral vector showed correction of the disease, but the studies were terminated after five subjects developed leukemia (four of whom were subsequently cured). Although none of our current product candidates utilize these gamma-retroviruses, our product candidates use a viral delivery system. Adverse events in our clinical studies, even if not ultimately attributable to our product candidates (such as the many adverse events that typically arise from the transplant process) and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

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

We are highly dependent on principal members of our executive team and key employees, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are “at will” employees. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical studies may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

As of January 31, 2016, we had 254 full-time employees. As our business activities expand, we expect to expand our full-time employee base and to hire more consultants and contractors. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy.

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, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA and non-U.S. regulators, provide accurate information to the FDA and non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, 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 may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical studies, which could result in regulatory sanctions and cause serious harm to our reputation or could cause regulatory agencies not to approve our product candidates. 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 governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical studies and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by subjects participating in clinical trials, consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical study participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry product liability insurance and we believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life-threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or 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 have a material adverse effect on the success of 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 generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use 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.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. 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. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We may not be successful in our efforts to identify or discover additional product candidates.

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our gene therapy and gene editing platforms. Although our LentiGlobin, Lenti-D and bb2121 product candidates are currently in clinical development, our research programs, including our oncology research programs, may fail to identify other 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 unmarketable or unlikely to receive marketing approval.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

We may use our financial and human resources to pursue a particular research program or product candidate and fail to capitalize on programs or product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs for product candidates 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 strategic 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, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

We incur significant costs as a result of operating as a public company, and our management devotes substantial time to new compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC, and The NASDAQ Global Select Market have imposed various requirements on public companies. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted, resulting in significant corporate governance and executive compensation-related regulations. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain our current levels of such coverage.

Risks related to our intellectual property

If we are unable to obtain or protect intellectual property rights related to our product candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates in the United States or in other foreign countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue and even if such patents cover our product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If the patent applications we hold or have in-licensed with respect to our programs or product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. Several patent applications covering our product candidates have been filed recently. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable

or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available however the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

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

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

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

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, ex parte reexaminations, post-grant review, and inter partes review proceedings before the U.S. Patent and Trademark Office, or U.S. PTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or

methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may not be successful in obtaining or maintaining necessary rights to gene therapy product components and processes for our development pipeline through acquisitions and in-licenses.

Presently we have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our gene therapy product candidates. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

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

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. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or

on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current product candidates or future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In many cases, patent prosecution of our licensed technology is controlled solely by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a licensing agreement, 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;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the 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.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

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

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The U.S. PTO is currently developing regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, were enacted March 16, 2013. However, it is not 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 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 have a material adverse effect on our business and financial condition.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors 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 our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. 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, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We have had in the past, and we may also have to in the future, ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the U.S. PTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our licensing partners initiated legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including patent eligible subject matter, 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 U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. 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, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore obtaining and enforcing biotechnology patents is costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have

narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the U.S. PTO, 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.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. 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 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 products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. 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 proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions 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 and 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 rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks related to ownership of our common stock

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the price at which you purchase them.

Companies trading in the stock market in general, and The NASDAQ Global Select Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and biotechnology and pharmaceutical industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

The market price of our common stock may be volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in preclinical or clinical studies;
- reports of adverse events in other gene therapy products or clinical studies of such products;
- inability to obtain additional funding;
- any delay in filing an IND or BLA for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA's review of that IND or BLA;
- failure to develop successfully and commercialize our product candidates;

- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;

- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic collaboration partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

Actual or potential sales of our common stock by our employees, including our executive officers, pursuant to pre-arranged stock trading plans could cause our stock price to fall or prevent it from increasing for numerous reasons, and actual or potential sales by such persons could be viewed negatively by other investors.

In accordance with the guidelines specified under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, and our policies regarding stock transactions, a number of our employees, including executive officers and members of our board of directors, have adopted and may continue to adopt stock trading plans pursuant to which they have arranged to sell shares of our common stock from time to time in the future. Generally, sales under such plans by our executive officers and directors require public filings. Actual or potential sales of our common stock by such persons could cause the price of our common stock to fall or prevent it from increasing for numerous reasons.

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

Additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2013 Stock Option and Incentive Plan, or the 2013 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2013 Plan automatically increases each year by up to 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors or compensation committee to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2013 Plan each year. If our board of directors or compensation committee elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall. We also have an Employee Stock Purchase Plan and any shares of common stock purchased pursuant to that plan will also cause dilution.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and resources, which could harm our business.

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

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to

offset its post-change income may be limited. We have completed several financings since our inception which we believe have resulted in a change in control as defined by IRC Section 382. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws, include provisions that:

- authorize “blank check” preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our corporate headquarters are located in Cambridge, Massachusetts. Our current leased facility encompasses approximately 53,500 square feet of office and laboratory space, located at 150 Second Street, Cambridge, Massachusetts. The nine-year lease

commenced in December 2013 and we have the option to extend this lease by an additional five years. We also lease 23,195 square feet of office space located at 215 First Street, Cambridge, Massachusetts, which lease expires between March 12, 2017 and July 12, 2020 at our option. In 2015 we also entered into a lease agreement for approximately 253,108 square feet of office and laboratory space located in a building under construction at 60 Binney Street, Cambridge, Massachusetts starting on October 1, 2016. The lease will continue until the end of the 120th full calendar month following April 2017 or the earlier the date we occupy the building or other conditions specified in the lease occur. We have the option to extend the 60 Binney Street lease for two successive five-year terms. We also lease approximately 7,800 square feet of office and laboratory space in Seattle, Washington, which lease expires in December 2016. We believe that our existing facilities are adequate for our current needs.

Item 3. Legal Proceedings

In the ordinary course of business, we are from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation relating to intellectual property, commercial arrangements and other matters. While the outcome of these proceedings and claims cannot be predicted with certainty, as of December 31, 2015, we were not party to any legal or arbitration proceedings that may have, or have had in the recent past, significant effects on our financial position or profitability. No governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

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

Our common stock has been traded on the Nasdaq Global Select Market under the symbol "BLUE." The following table shows the high and low sale prices per share of our common stock as reported on the Nasdaq Global Select Market for the periods indicated:

	High	Low
2014		
First Quarter 2014	$28.08	$19.34
Second Quarter 2014	$41.75	$17.40
Third Quarter 2014	$40.31	$30.33
Fourth Quarter 2014	$94.77	$29.73
2015		
First Quarter 2015	$128.88	$83.00
Second Quarter 2015	$197.35	$116.00
Third Quarter 2015	$171.24	$82.05
Fourth Quarter 2015	$106.95	$48.85

On February 18, 2016, the last reported sale price for our common stock on the Nasdaq Global Select Market was $52.10 per share.

Stock Performance Graph

The graph set forth below compares the cumulative total stockholder return on our common stock between June 19, 2013 (the date of our initial public offering) and December 31, 2015, 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 June 19, 2013 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 June 19, 2013 of $26.91 per share as the initial value of our common stock and not the initial offering price to the public of $17.00 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 stock. 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 February 18, 2016, there were approximately 19 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

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

Recent Sales of Unregistered Securities

During the year ended December 31, 2015, we issued an aggregate of 164,049 shares of common stock pursuant to the cashless net exercise of outstanding warrants exercisable for 177,276 shares of our common stock held by an existing investor. Such sale of securities were made in reliance upon the exemption from registration provided by Section 4(a)(2) of the Securities Act of 1933, as amended, for transactions by an issuer not involving a public offering. The foregoing securities are deemed restricted securities for the purposes of the Securities Act of 1933, as amended.

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.

Purchases of Equity Securities by the Issuer

We repurchased the following shares in the periods set forth in the table below:

Period	Total Number of Shares (or Units) Purchased	Average Price Paid per Share (or Unit)	Total Number of Shares (or Units) Purchased as Part of Publicly Announced Plan or Program	Maximum Number (or Approximate Dollar Value) of Shares (or Units) that May Yet Be Purchased Under the Plans or Programs
July 1 to July 31, 2015 (a)	628	$ 158.91	—	—
August 1 to August 31, 2015 (b)	239	$ 135.89	—	—
Total	867		—	

(a) Our 2013 Stock Option and Incentive Plan (“Option Plan”), permits participants to use the fair market value of our common stock they own to pay for the exercise of stock options (“stock swap method”). In connection with the exercise of a stock option to purchase 2,500 shares of our common stock at an exercise price of $39.89 per share, an optionee tendered 628 shares of our common stock held by the optionee in consideration of the full aggregate exercise price in accordance with the terms of the option and the Option Plan. The shares used under the stock swap method are included in the total number of shares purchased in the table above.

(b) In connection with the exercise of a stock option to purchase 812 shares of our common stock at an exercise price of $39.89 per share, an optionee tendered 239 shares of our common stock held by the optionee in consideration of the full aggregate exercise price in accordance with the terms of the option and the Option Plan. The shares used under the stock swap method are included in the total number of shares purchased in the table above.

Item 6. Selected 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.

We derived the consolidated financial data for the years ended December 31, 2015, 2014 and 2013 and as of December 31, 2015 and 2014 from our audited consolidated financial statements, which are included elsewhere in this Annual Report on Form 10-K. We derived the consolidated financial data for the years ended December 31, 2012 and 2011 and as of December 31, 2012 and 2011 from our audited consolidated financial statements that are not included elsewhere 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,				
	2015	2014 (1)	2013	2012	2011
	(in thousands, except per share amounts)				
Consolidated statements of operations data:					
Revenue:					
Collaboration revenue	$14,079	$25,031	$19,792	$—	$—
Research and license fees	—	390	389	340	640
Grant revenue	—	—	—	—	242
Total revenue	14,079	25,421	20,181	340	882
Expenses:					
Research and development	134,038	62,574	31,002	17,210	11,409
General and administrative	46,209	23,227	14,126	6,846	4,615
Change in fair value of contingent consideration	2,869	246	—	—	—
Total operating expenses	183,116	86,047	45,128	24,056	16,024
Loss from operations	(169,037)	(60,626)	(24,947)	(23,716)	(15,142)
Other income (expense), net	2,314	120	(374)	46	(456)
Income tax (expense) benefit	(60)	11,797	—	—	—
Net loss	$(166,783)	$(48,709)	$(25,321)	$(23,670)	$(15,598)
Net loss per share applicable to common stockholders - basic and diluted	$(4.81)	$(1.83)	$(2.02)	$(13.79)	$(171.59)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	34,669	26,546	12,555	262	120

	As of December 31,				
	2015	2014 (1)	2013	2012	2011
	(in thousands)				
Consolidated balance sheet data:					
Cash and cash equivalents	$164,269	$347,845	$206,279	$67,011	$25,604
Marketable securities	701,494	144,158	—	—	3,507
Working capital	483,597	437,011	177,113	63,156	27,087
Total assets	1,002,337	556,739	224,390	69,322	30,918
Construction financing lease obligation	61,901	—	—	—	—
Other long-term obligations	49,572	22,504	37,849	601	1,329
Preferred stock	—	—	—	122,177	82,403
Common stock and additional paid-in capital	1,166,954	638,712	250,342	15,270	7,734

Total stockholders' equity (deficit)	850,496	491,257	151,667	(55,747)	(55,707)

(1) Starting in 2014, the selected financial data includes the impact of the acquisition of Pregenen in June 2014. See Note 11. “Business Combinations” in the accompanying notes to consolidated financial statements for additional information.

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

The following information should be read in conjunction with the consolidated financial statements and related notes thereto included in this Annual Report on Form 10-K

Except for the historical information contained herein, the matters discussed in this Annual Report on Form 10-K may be deemed to be forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. In this Annual Report on Form 10-K, words such as "may," "expect," "anticipate," "estimate," "intend," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements.

Our actual results and the timing of certain events may differ materially from the results discussed, projected, anticipated, or indicated in any forward-looking statements. We caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this Annual Report. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this Annual Report, they may not be predictive of results or developments in future periods.

The following information and any forward-looking statements should be considered in light of factors discussed elsewhere in this Annual Report on Form 10-K, including those risks identified under Item 1A. Risk Factors.

We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

Overview

We are a clinical-stage biotechnology company committed to developing potentially transformative gene therapies for severe genetic and rare diseases and in the field of T cell-based immunotherapy. With our lentiviral-based gene therapy and gene editing capabilities, we have built an integrated product platform with broad potential application in these areas. We believe that gene therapy for severe genetic diseases has the potential to change the way these patients are treated by correcting the underlying genetic defect that is the cause of their disease, rather than offering treatments that only address their symptoms. We and our scientific collaborators have generated what we believe is human proof-of-concept data for our gene therapy platform in three underserved diseases.

We are conducting three clinical studies of our LentiGlobin product candidate: a Phase I/II study in the United States, Australia, and Thailand, called the Northstar Study, for the treatment of transfusion-dependent -thalassemia, or TDT; a single-center Phase I/II study in France (HGB-205) for the treatment of TDT and severe sickle cell disease, or severe SCD; and a Phase I study in the United States (HGB-206) for the treatment of severe SCD. Both TDT and severe SCD are rare, hereditary blood disorders that often lead to severe anemia and shortened lifespans. Our LentiGlobin product candidate has been granted Orphan Drug status by the U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, for both -thalassemia and SCD. Our LentiGlobin product candidate was granted Fast-Track designation by the FDA for the treatment of -thalassemia major in January 2013 and for the treatment of certain patients with severe SCD in May 2014. In January 2015, the FDA granted Breakthrough Therapy designation to our LentiGlobin product candidate for the treatment of transfusion-dependent patients with -thalassemia major. We have discussed the designs of two global Phase III clinical trials of our LentiGlobin product candidate for patients with TDT with the FDA and EMA. We expect that our HGB-207 study will enroll patients with TDT who do not have

the $^{0}/^{0}$ genotype for adult and adolescent patients, and once initiated, is currently expected to enroll approximately 15 patients to be evaluated for 24 months following treatment. We anticipate that the primary endpoint of this study will be 12 months of transfusion independence following treatment. In addition, we are considering initiating an additional Phase III clinical study in pediatric patients who have a diagnosis of TDT.

We are also conducting a Phase II/III clinical study, called the Starbeam Study, of our Lenti-D product candidate, to evaluate its safety and efficacy in subjects with cerebral adrenoleukodystrophy, or CALD, a rare, hereditary neurological disorder that is often fatal. In October 2013, we announced that the first subject had been treated in this study and in May 2015 we announced the achievement of enrollment of 18 subjects in this study. We are also conducting an observational study of subjects with CALD treated by allogeneic hematopoietic stem-cell transplant referred to as the ALD-103 study. Our Lenti-D product candidate has been granted Orphan Drug status by the FDA and the EMA for the treatment of adrenoleukodystrophy.

In March 2013, we entered into a global strategic collaboration with Celgene Corporation, or Celgene, to discover, develop and commercialize chimeric antigen receptor-modified T cells, or CAR T cells, as potentially disease-altering therapies in oncology. This collaboration had an initial term of three years, and Celgene made a $75.0 million up-front, non-refundable cash payment to us as

consideration for entering into the collaboration. In June 2015, we amended and restated the collaboration agreement, or the Amended Collaboration Agreement, to focus exclusively on anti-BCMA product candidates for a new three-year term. B-cell maturation antigen, or BCMA, is a cell surface protein that is expressed on normal plasma cells and on most multiple myeloma cells, but is absent from other normal tissues. As consideration for the Amended Collaboration Agreement, we received an upfront, non-refundable cash payment of $25.0 million to fund research and development under the collaboration. During the year ended December 31, 2015, we recognized $14.1 million of revenue associated with our collaboration with Celgene related to the research and development services performed. As of December 31, 2015, we have classified $41.8 million of deferred revenue related to our collaboration with Celgene as current or long-term in the accompanying balance sheets based on the contractual term of the arrangement. In February 2016, we initiated a Phase I clinical study of bb2121, the first anti-BCMA product candidate from this collaboration. This study will enroll up to 40 patients who have received three prior regimens for treatment of multiple myeloma. In February 2016, Celgene exercised its option to obtain an exclusive worldwide license to develop and commercialize bb2121 and as a result, will pay to us an option fee in the amount of $10.0 million in the first quarter of 2016. We may elect to co-develop and co-promote bb2121, and any other product candidates in the United States under this collaboration arrangement.

In June 2014, we acquired Precision Genome Engineering, Inc., or Pregenen, a privately-held biotechnology company headquartered in Seattle, Washington. Through the acquisition, we obtained rights to Pregenen's gene editing and cell signaling technology. The agreement provides for up to $135.0 million in future contingent cash payments by us upon the achievement of certain preclinical, clinical and commercial milestones related to the Pregenen technology, of which $15.0 million relates to preclinical milestones, $20.1 million relates to clinical milestones and $99.9 million relates to commercial milestones. During 2015, a $1.0 million milestone was achieved and paid to the former equityholders of Pregenen. We estimate future contingent cash payments have a fair value of $8.7 million as of December 31, 2015, $3.6 million of which is classified as a current liability.

As of December 31, 2015, we had cash, cash equivalents and marketable securities of approximately $865.8 million. We expect that our existing cash, cash equivalents and marketable securities will be sufficient to fund our current operations through 2018.

Since our inception in 1992, we have devoted substantially all of our resources to our development efforts relating to our product candidates, including activities to manufacture product candidates in compliance with good manufacturing practices, or GMP, to conduct clinical studies of our product candidates, to provide general and administrative support for these operations and to protect our intellectual property. We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations primarily through the sale of common stock in our public offerings, private placements of preferred stock and warrants and through collaborations.

We have never been profitable and have incurred net losses in each year since inception. Our net losses were $166.8 million for the year ended December 31, 2015 and our accumulated deficit was $314.2 million as of December 31, 2015. Substantially all our net losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We expect our expenses will increase substantially in connection with our ongoing and planned activities, as we:

- conduct clinical studies for our LentiGlobin, Lenti-D, and bb2121 product candidates;
- increase research and development-related activities for the discovery and development of oncology product candidates;
- continue our research and development efforts;
- manufacture clinical study materials and develop large-scale manufacturing capabilities;
- seek regulatory approval for our product candidates; and
- add personnel to support our product development and commercialization efforts.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates, which we expect will take a number of years and is subject to significant uncertainty. We have no commercial-scale manufacturing facilities, and all of our manufacturing activities are contracted out to third parties. Additionally, we currently utilize third-party contract research organizations, or CROs, to carry out our clinical development activities; and we do not yet have a sales and marketing organization. If we seek to obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses as we prepare for product sales, marketing, manufacturing, and distribution. Accordingly, we will seek to fund our operations through public or private equity or debt financings, strategic collaborations, or other sources. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our products.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenues from the sale of our products, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Financial operations overview

Revenue

To date, we have not generated any revenues from the sale of products. Our revenues have been derived from collaboration arrangements, research fees, license fees and grant revenues.

Collaboration revenue is generated exclusively from our collaboration arrangement with Celgene, which was amended in 2015. The terms of this amended arrangement contain multiple deliverables, which include at inception: (i) research and development services, (ii) participation on the joint steering committee, or JSC, (iii) participation on the patent committee, (iv) a license to the first product candidate, (v) manufacture of vectors and associated payload for incorporation into the first optioned product candidate under the license, and (vi) participation on the joint governance committee, or JGC, under the co-development and co-promotion agreement for the first optioned product candidate under the license. We recognize arrangement consideration allocated to each unit of accounting when all of the revenue recognition criteria in Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 605, Revenue Recognition, or ASC 605, are satisfied for that particular unit of accounting. Revenue from the Celgene arrangement associated with discovery, research and development services, joint steering committee services and patent committee services is recognized ratably over the associated period of performance, which is initially three years.

Research and license fee revenue is primarily generated through license and research and development agreements with strategic partners and nonprofit organizations for the development and commercialization of our product candidates. There are no performance, cancellation, termination, or refund provisions in any of our arrangements that contain material financial consequences to us.

Nonrefundable license fees are recognized as revenue upon delivery provided there are no undelivered elements in the arrangement. Research fees are recognized as revenue over the period we perform the associated services or on a straight-line basis if the pattern of performance cannot be estimated.

Research and development expenses

Research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with CROs and clinical sites that conduct our clinical studies;
- costs of acquiring, developing, and manufacturing clinical study materials;
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other supplies;
- costs associated with our research platform and preclinical activities;
- costs associated with our regulatory, quality assurance and quality control operations; and
- amortization of intangible assets.

Research and development costs are expensed as incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites. We cannot determine with certainty the duration and completion costs of the current

or future clinical studies of our product candidates or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs, and timing of clinical studies and development of our product candidates will depend on a variety of factors, including:

- the scope, rate of progress, and expense of our ongoing as well as any additional clinical studies and other research and development activities we undertake;
- future clinical study results;

- uncertainties in clinical study enrollment rates;
- changing standards for regulatory approval; and
- the timing and receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA, or another regulatory authority were to require us to conduct clinical studies beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate or if we experience significant delays in enrollment in any of our clinical studies, we could be required to expend significant additional financial resources and time on the completion of clinical development for our product candidates.

From inception through December 31, 2015, we have incurred $292.1 million in research and development expenses. We plan to increase our research and development expenses for the foreseeable future as we continue to advance the development of our Lenti-D, LentiGlobin, and bb2121 product candidates, conduct research and development activities in oncology, including under our strategic collaboration with Celgene, and continue the research and development of product candidates using our gene editing technology platform. Our research and development activities include the following:

- We are conducting a Phase II/III clinical study to examine the safety and efficacy of our Lenti-D product candidate in the treatment of CALD. In October 2013, we announced that the first subject had been treated in this study.
- We are conducting a Phase I/II clinical study in the United States, Australia and Thailand to study the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with TDT. In March 2014, we announced that the first subject had been treated in this study.
- We are conducting a Phase I/II clinical study in France to study the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with TDT and severe SCD. In December 2013, we announced that the first subject with TDT had been treated in this study and in October 2014, we announced that the first subject with severe SCD had been treated in this study.
- We are conducting a Phase I clinical study in the United States to study the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with severe SCD. In June 2015, we announced that the first subject with severe SCD had been treated in this study.
- We are conducting a Phase I clinical study in the United States to study the safety and efficacy of our bb2121 product candidate in the treatment of subjects with relapsed/refractory multiple myeloma. In February 2016, we announced that the first subject with relapsed/refractory multiple myeloma had been treated in this study.
- We will continue to manufacture clinical study materials in support of our clinical studies.

Our direct research and development expenses consist principally of external costs, such as fees paid to investigators, consultants, central laboratories and CROs in connection with our clinical studies, and costs related to acquiring and manufacturing clinical study materials. Effective January 1, 2014, we began allocating salary and benefit costs directly related to specific programs. We do not allocate personnel-related discretionary bonus or stock-based compensation costs, costs associated with our general discovery platform improvements, depreciation or other indirect costs that are deployed across multiple projects under development and, as such, the costs are separately classified as personnel and other expenses in the table below:

	Year ended December 31,		
	2015	2014	2013
	(in thousands)		
LentiGlobin	$38,515	$21,444	$8,490
Lenti-D	13,666	12,137	4,396
Pre-clinical programs	15,937	6,651	783
Total direct research and development expense	68,118	40,232	13,669
Employee- and contractor-related expenses	11,793	6,771	9,152

Stock-based compensation expense	24,854	5,151	3,809
Platform-related expenses	21,217	5,112	1,067
Facility expenses	7,282	5,292	2,288
Other expenses	774	16	1,017
Unallocated personnel and other expenses	65,920	22,342	17,333
Total research and development expense	$134,038	$62,574	$31,002

General and administrative expenses

General and administrative expenses consist primarily of salaries and related costs for personnel, including stock-based compensation and travel expenses for our employees in executive, operational, finance, legal, business development, commercial and human resource functions. Other general and administrative expenses include facility-related costs, professional fees for accounting, tax and legal and consulting services, directors' fees and expenses associated with obtaining and maintaining patents.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research and development and potential commercialization of our product candidates. Additionally, if and when we believe a regulatory approval of the first product candidate appears likely, we anticipate an increase in payroll and related expenses as a result of our preparation for commercial operations, especially as it relates to the sales and marketing of our product candidates.

Other income (expense), net

Other income and expense consists primarily of interest income earned on investments, the gain or loss associated with the change in the fair value of preferred stock warrants, foreign currency gain or loss and tax incentives from the Massachusetts Life Sciences Center. In 2015, we received $0.9 million related to the disgorgement of short-swing profits arising from trades by a bluebird officer under Section 16(b) of the Securities Exchange Act of 1934, as amended.

Until our IPO in June 2013 when all our outstanding preferred stock warrants were converted into common stock warrants, we recognized the re-measurement gain or loss associated with the change in the fair value of the preferred stock warrant liability as a component of other income (expense), net. We used the Black-Scholes option pricing model to estimate the fair value of preferred stock warrants. We based the estimates in the Black-Scholes option pricing model, in part, on subjective assumptions, including stock price volatility, risk-free interest rate, dividend yield, and the fair value of the preferred stock underlying the warrants.

Critical accounting policies and significant judgments and estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued research and development expenses, stock-based compensation, and business combinations. We base our estimates on historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. In making estimates and judgments, management employs critical accounting policies.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this annual report, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

Revenue recognition

We have primarily generated revenue through collaboration arrangements, research arrangements and license arrangements with strategic partners and nonprofit organizations for the development and commercialization of

product candidates. Additionally, we have generated revenue from research and development grant programs.

We recognize revenue in accordance with 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
- Collectability is reasonably assured

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue in our consolidated balance sheets. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, current portion. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, net of current portion.

Collaboration revenue

As of December 31, 2015, our collaboration revenue was generated exclusively from our collaboration arrangement with Celgene. The terms of this arrangement contains multiple deliverables, which include at inception: (i) research and development services, (ii) participation on the JSC, (iii) participation on the patent committee, (iv) a license to the first product candidate, (v) manufacture of vectors and associated payload for incorporation into the first optioned product candidate under the license, and (vi) participation on the JGC under the co-development and co-promotion agreement for the first optioned product candidate under the license. Non-refundable payments to us under this arrangement may include: (i) up-front research fees, (ii) product candidate license fees, (iii) payments for the manufacture and supply of vectors and payloads, (iv) payments based on the achievement of certain milestones and (v) royalties on product sales. Additionally, we may elect to share in the costs incurred from the development, commercialization and manufacture of product candidates licensed by our collaborators and earn our share of the net profits or bear our share of the net losses generated from the sale of product candidates licensed by our collaborators.

We analyze multiple-element arrangements based on the guidance in FASB ASC Topic 605-25, Revenue Recognition-Multiple-Element Arrangements, or ASC 605-25. Pursuant to the guidance in ASC 605-25, we evaluate multiple-element arrangements to determine (1) the deliverables included in the arrangement and (2) whether the individual deliverables represent separate units of accounting or whether they must be accounted for as a combined unit of accounting. This evaluation involves subjective determinations and 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(s) has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially in our control. In assessing whether an item has standalone value, we consider factors such as the research, 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 the other deliverable(s) for their intended purpose without the receipt of the remaining element(s), whether the value of the deliverable is dependent on the undelivered item(s) and whether there are other vendors that can provide the undelivered element(s). The collaboration arrangement does not contain a general right of return relative to the delivered item(s).

Arrangement consideration that is fixed or determinable is allocated among the separate units of accounting using the relative selling price method. Then, the applicable revenue recognition criteria in ASC 605 are applied to each of the separate units of accounting in determining the appropriate period and pattern of recognition. We determine the selling price of a unit of accounting following the hierarchy of evidence prescribed by ASC 605-25. Accordingly, we determine the estimated selling price for units of accounting within each arrangement using vendor-specific objective evidence, or VSOE, of selling price, if available, third-party evidence, or TPE, of selling price if VSOE is not available, or best estimate of selling price, or BESP, if neither VSOE nor TPE is available. We typically use BESP to estimate the selling price, since we generally do not have VSOE or TPE of selling price for our units of accounting. Determining the BESP for a unit of accounting requires significant judgment. In developing the BESP 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 BESP 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.

Options are considered substantive if, at the inception of the arrangement, we are at risk as to whether the collaboration partner will choose to exercise the option. Factors that we consider in evaluating whether an option is substantive include the overall objective of the arrangement, the benefit the collaborator might obtain from the arrangement without exercising the option, the cost to exercise the option and the likelihood that the option will be exercised. For arrangements under which an option is considered substantive, we do not consider the item underlying the option to be a deliverable at the inception of the arrangement and the associated option fees are not included in allocable arrangement consideration, assuming the option is not priced at a significant and incremental discount.

Conversely, for arrangements under which an option is not considered substantive or if an option is priced at a significant and incremental discount, we would consider the item underlying the option to be a deliverable at the inception of the arrangement and a corresponding amount would be included in allocable arrangement consideration. The license to the first product candidate is considered a deliverable at the inception of the arrangement but options to license any additional product candidates are substantive options and therefore are not considered deliverables at inception.

We recognize arrangement consideration allocated to each unit of accounting when all of the revenue recognition criteria in ASC 605 are satisfied for that particular unit of accounting. We will recognize as revenue arrangement consideration attributed to licenses that have standalone value from the other deliverables to be provided in an arrangement upon delivery. We will recognize as revenue arrangement consideration attributed to licenses that do not have standalone value from the other deliverables to be provided in an arrangement over our estimated performance period as the arrangement would be accounted for as a single unit of accounting.

We recognize revenue from the Celgene arrangement associated with discovery, research and development services, joint steering committee services and patent committee services ratably over the associated period of performance. If there is no discernible pattern

of performance and/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 expect to complete our performance obligations. Conversely, if the pattern of performance in 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.

At the inception of an arrangement that includes milestone payments, 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(s) 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 respective milestone and the level of effort and investment required to achieve the respective 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 have concluded that all of the clinical and regulatory milestones pursuant to its collaboration arrangement are substantive. Accordingly, in accordance with FASB ASC Topic 605-28, Revenue Recognition-Milestone Method, revenue from clinical and regulatory milestone payments will be recognized in its entirety upon successful accomplishment of the milestone, assuming all other revenue recognition criteria are met. Milestones that are not considered substantive would be recognized as revenue over the remaining period of performance, assuming all other revenue recognition criteria are met. Revenue from commercial milestone payments will be accounted for as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.

We 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 we have no remaining performance obligations, assuming all other revenue recognition criteria are met.

Intangible assets

Intangible assets consist of acquired core technology with finite lives. We amortize intangible assets using the straight-line method over their estimated economic lives. We evaluate the potential impairment of intangible assets if events or changes in circumstances indicate that the carrying amount of the assets may not be fully recoverable or that the useful lives of these assets are no longer appropriate. The impairment test is based on a comparison of the undiscounted cash flows expected to be generated from the use of the asset group and its eventual disposition to the carrying value of the asset group. If impairment is indicated, the asset is written down by the amount by which the carrying value of the asset exceeds the related fair value of the asset. We have not recognized an impairment charge related to intangible assets.

Construction financing lease obligation

Beginning in 2015 and until construction completion, we record certain estimated construction costs incurred and reported to us by the landlord for our 60 Binney Street location as an asset and corresponding construction financing lease obligation on the consolidated balance sheets because we are deemed to be the owner of the building during the construction period for accounting purposes. Any incremental costs incurred directly by us are also capitalized. In each reporting period, the landlord estimates and reports to us costs incurred to date related to our portion of the building using allocation estimates and provides supporting invoices for our review. We periodically meet with the landlord and its construction manager to review these estimates and observe construction progress before recording such amounts.

Contingent consideration

Each reporting period, we revalue the contingent consideration obligations associated with business combinations to their fair value and record increases in their fair value as contingent consideration expense and decreases in the fair value as contingent consideration income. Changes in contingent consideration result from changes in the assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones are achieved and the discount rate used to estimate the fair value of the liability. Contingent consideration may change significantly as development of our programs progress and additional data are obtained, impacting our assumptions. The assumptions used in estimating fair value require significant judgment and the use of different assumptions and judgments could result in a materially different estimate of fair value.

Accrued research and development expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been

performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

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

We base our expenses related to clinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differs from the actual status and timing of services performed we may report amounts that are too high or too low in any particular period. To date, there has been no material differences from our estimates to the amount actually incurred.

Stock-based compensation

Stock-based awards

We issue stock-based awards to employees and non-employees, generally in the form of stock options and restricted stock units. We account for our stock-based awards in accordance with FASB ASC Topic 718, Compensation—Stock Compensation, or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. We account for stock-based awards to non-employees in accordance with FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees, which requires the fair value of the award to be re-measured at fair value as the award vests.

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

Described below is the methodology we have utilized in measuring stock-based compensation expense. Following the consummation of our initial public offering, stock option and restricted stock unit values have been determined based

on the quoted market price of our common stock.

We estimate the fair value of our stock-based awards to employees and non-employees using the Black-Scholes option pricing model, which requires the input of highly subjective assumptions, including (i) the expected volatility of our stock, (ii) the expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Due to the lack of a public market for the trading of our common stock 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. For these analyses, we select companies with comparable characteristics to ours including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own

stock price becomes available. We estimate the expected life of our employee stock options using the "simplified" method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option were based on the U.S. Treasury yield curve in effect during the period the options were granted.

We are also required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from its estimates. We use historical data to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from our estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.

We have computed the fair value of employee and director stock options at date of grant using the following weighted-average assumptions:

	Year ended December 31,		
	2015	2014	2013
Expected volatility	72.6%	82.3%	82.0%
Expected term (in years)	5.9	6.0	6.1
Risk-free interest rate	1.7%	1.8%	1.1%
Expected dividend yield	0.0%	0.0%	0.0%
Weighted average exercise price per share	$113.37	$26.92	$8.59

Stock-based compensation totaled approximately $41.1 million for the year ended December 31, 2015 and $10.8 million for the year ended December 31, 2014. As of December 31, 2015, we had $80.7 million of total unrecognized compensation expense related to unvested stock options, net of related forfeiture estimates, which is expected to be recognized over a weighted-average remaining vesting period of approximately 2.9 years and $6.2 million of total unrecognized compensation expenses related to unvested restricted stock units, net of related forfeiture estimates, which is expected to be recognized over a weighted-average remaining vesting period of 2.2 years. We expect the impact of our stock-based compensation expense for stock options and restricted stock units granted to employees and non-employees to grow in future periods due to the current year and potential future increases in the value of our common stock and headcount.

Recent accounting pronouncements

See Note 2 to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this Annual Report on Form 10-K for a description of recent accounting pronouncements applicable to our business.

Results of Operations

Comparison of the years ended December 31, 2015 and 2014:

	Year ended December 31,		
	2015	2014	Change

	(in thousands)		
Revenue:			
Collaboration revenue	$14,079	$25,031	$(10,952)
Research and license fees	—	390	(390)
Total revenue	14,079	25,421	(11,342)
Operating expenses:			
Research and development	134,038	62,574	71,464
General and administrative	46,209	23,227	22,982
Change in fair value of contingent consideration	2,869	246	2,623
Total operating expenses	183,116	86,047	97,069
Loss from operations	(169,037)	(60,626)	108,411
Other income (expense), net	2,314	120	(2,194)
Loss before income taxes	(166,723)	(60,506)	106,217
Income tax (expense) benefit	(60)	11,797	11,857
Net loss	$(166,783)	$(48,709)	$118,074

Revenue. Total revenue was $14.1 million for the year ended December 31, 2015, compared to $25.4 million for the year ended December 31, 2014. The decrease of $11.3 million was primarily due to a change in revenue recognition resulting from the amendment to our Celgene collaboration in 2015.

Research and development expenses. Research and development expenses were $134.0 million for the year ended December 31, 2015, compared to $62.6 million for the year ended December 31, 2014. The increase of $71.5 million was primarily due to the increase in headcount, in-licensing costs, clinical trial-related costs, and manufacturing-related expenses necessary to support the advancement of our product candidates into clinical trials and included the following increases:

- Direct research and development expenses:
- $31.3 million of employee compensation and benefits, of which $19.7 million was related to stock-based compensation expense ($10.1 million of which is non-recurring and related to modifications of awards of a non-employee founder and two former employees) and $7.3 million related to increased payroll expense related to increased headcount to support our advancing pipeline.
- $12.0 million of non-recurring in-license milestones and fees, of which $5.4 million related to an upfront payment for amending and restating an existing patent sublicense agreement; $3.3 million (€3.0 million) related to an upfront payment for amending an existing license agreement with Institut Pasteur; and $2.5 million related to upfront payments for new license agreements with collaborators to support our preclinical oncology programs.
- $8.9 million of manufacturing costs for our ongoing clinical and pre-clinical studies.
- $5.3 million of clinical trial-related costs to support the advancement of our clinical programs.
- $4.9 million of direct project laboratory supplies related to increased headcount and process development activities.
- Other expenses:
- $1.9 million in amortization of our gene editing platform intangible asset related to our acquisition of Pregenen in mid-2014.
- $1.9 million in expenses related to ongoing collaboration research agreements.

General and administrative expenses. General and administrative expenses were $46.2 million for the year ended December 31, 2015, compared to $23.2 million for the year ended December 31, 2014. The increase of $23.0 million was primarily due to the following increases in expenses: $15.1 million of employee-related costs to support our overall growth, of which $10.6 million was related to stock-based compensation expense and $2.5 million was related increased payroll expense due to increased headcount; $2.3 million of consulting costs to support our overall growth; $1.2 million in rent and other facility-related expenses related to accommodate increased headcount; $1.1 million of commercial market research and $1.1 million of professional fees.

Change in fair value of contingent consideration. The change in fair value of contingent consideration of $2.6 million was primarily related to the successful achievement of a milestone in 2015 and an increase in the probability of successful achievement of future milestones expected to be achieved within the next twelve months.

Other income (expense), net. Other income (expense), net, was $2.3 million for the year ended December 31, 2015, compared to $0.1 million for the year ended December 31, 2014. The increase of $2.2 million was primarily related to interest income earned on marketable securities purchased in the second half of 2015 and income from the disgorgement of short-swing profits arising from trades by a bluebird officer under Section 16(b) of the Securities Exchange Act of 1934.

Income tax (expense) benefit. The change in income tax (expense) benefit was primarily attributable to a non-recurring tax benefit recognized in 2014 as a result of the acquisition of Pregenen.

Comparison of the years ended December 31, 2014 and 2013:

	Year ended December 31,		
	2014	2013	Change
	(in thousands)		
Revenue:			
Collaboration revenue	$25,031	$19,792	$5,239
Research and license fees	390	389	1
Total revenue	25,421	20,181	5,240
Operating expenses:			
Research and development	62,574	31,002	31,572
General and administrative	23,227	14,126	9,101
Change in fair value of contingent consideration	246	—	246
Total operating expenses	86,047	45,128	40,919
Loss from operations	(60,626)	(24,947)	35,679
Other income (expense), net	120	(374)	(494)
Loss before income taxes	(60,506)	(25,321)	35,185
Benefit from income taxes	11,797	—	(11,797)
Net loss	$(48,709)	$(25,321)	$23,388

Revenue. Total revenue was $25.4 million for the year ended December 31, 2014, compared to $20.2 million for the year ended December 31, 2013. The increase of $5.2 million was primarily due to a full year of revenue from our Celgene collaboration, which was signed on March 19, 2013 and was expected to be recognized on a straight-line basis through March 2016.

Research and development expenses. Research and development expenses were $62.6 million for the year ended December 31, 2014, compared to $31.0 million for the year ended December 31, 2013. The increase of $31.6 million was primarily due to the increase in headcount, clinical trial-related costs and manufacturing-related expenses necessary to support the advancement of our product candidates into clinical trials, as well as expenses for the Celgene collaboration, and included the following increases in expenses:

- Direct research and development expenses:
- $8.4 million of employee compensation and benefits, of which $1.3 million was related to stock-based compensation expense.
- $6.8 million of manufacturing costs for our ongoing clinical studies.
- $6.3 million of clinical trial-related costs.
- $2.9 million of direct project laboratory supplies related to increased headcount and process development activities.
- $1.0 million of license fees.
- Other expenses:
    - $2.5 million in rent and other facility-related expenses related to our new corporate headquarters.
- $1.9 million in amortization of our gene editing platform intangible asset related to our acquisition of Pregenen.
- $0.8 million in expenses related to ongoing collaboration agreements.
- $0.8 million in costs associated with preclinical research activities.

General and administrative expenses. General and administrative expenses were $23.2 million for the year ended December 31, 2014, compared to $14.1 million for the year ended December 31, 2013. The increase of $9.1 million was primarily due to the following increases in expenses: $5.9 million of employee-related costs to support our overall

growth, of which $2.4 million was related to stock-based compensation expense and $0.8 million was related to a one-time severance charge; $1.0 million of professional fees to support the requirements of being a public company; $0.2 million in rent and other facility-related expenses related to our new corporate headquarters to accommodate increased headcount; $0.7 million in general office expenses as a result of increased headcount and $0.9 million in depreciation and amortization relating to our fixed assets, including our new corporate headquarters.

Change in fair value of contingent consideration. The change in fair value of contingent consideration of $0.2 million was related to the acquisition of Pregenen in 2014.

Other income (expense), net. Other income (expense), net, was $0.1 million for the year ended December 31, 2014, compared to $(0.4) million for the year ended December 31, 2013. The decrease of $0.5 million was primarily due to the re-measurement of fair value of our convertible preferred stock warrants in 2013, foreign currency gain and interest income.

Benefit from income taxes. The increase in income tax benefit was attributable to a non-recurring tax benefit recognized in 2014 as a result of the acquisition of Pregenen.

Liquidity and Capital Resources

As of December 31, 2015, we had cash, cash equivalents and marketable securities of approximately $865.8 million. We expect cash, cash equivalents and marketable securities to fund operations through 2018. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. As of December 31, 2015, our funds are held in U.S. Treasury securities, U.S. government agency securities, federally insured deposits, certificates of deposit and money market funds.

We have incurred losses and cumulative negative cash flows from operations since our inception in April 1992, and as of December 31, 2015, we had an accumulated deficit of $314.2 million. We anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through public or private equity or debt financings, strategic collaborations, or other sources.

We have funded our operations principally from the sale of common stock, preferred stock and through the Celgene collaboration. On June 24, 2013, we completed our initial public offering, or IPO, whereby we sold 6,832,352 shares of common stock at a price of $17.00 per share for aggregate net proceeds received by us of $104.9 million. On July 14, 2014, we sold 3,450,000 shares of common stock (inclusive of 450,000 shares of common stock sold by us pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $34.00 per share for aggregate net proceeds to us of $109.8 million. On December 19, 2014, we sold 3,047,500 shares of common stock (inclusive of 397,500 shares of common stock sold by us pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $85.00 per share for aggregate net proceeds to us of $243.3 million. On June 29, 2015, we sold 2,941,176 shares of common stock through an underwritten public offering at a price of $170.00 per share for aggregate net proceeds to us of $477.2 million.

Sources of Liquidity

Cash Flows

The following table sets forth the primary sources and uses of cash for each of the periods below:

	Year ended December 31,		
	2015	2014	2013
	(in thousands)		
Net cash provided by (used in):			
Operating activities	$(98,429)	$(59,693)	$43,450
Investing activities	(571,867)	(157,193)	(9,823)
Financing activities	486,720	358,452	105,641
Net (decrease) increase in cash and cash equivalents	$(183,576)	$141,566	$139,268

Cash Flows from Operating Activities. The net cash used in operating activities was $98.4 million for the year ended December 31, 2015 and primarily consisted of a net loss of $166.8 million adjusted for non-cash items including stock-based compensation of $41.1 million, depreciation and amortization of $7.4 and a net increase in operating assets and liabilities of $16.0 million. The significant items in the increase in operating assets and liabilities include an increase in deferred revenue of $11.2 million related to the amendment to our collaboration with Celgene and an increase in accrued expenses of $9.4 million related to an increase in accrued goods and services and an increase in the contingent consideration, offset by a decrease in prepaid expenses and other assets of $6.8 million due to purchases of marketable securities at a premium.

The net cash used in operating activities was $59.7 million for the year ended December 31, 2014 and primarily consisted of a net loss of $48.7 million adjusted for non-cash items including a noncash benefit on release of tax valuation allowance of $11.8 million, stock-based compensation of $10.8 million, depreciation and amortization of $4.2 and a net decrease in operating assets and liabilities of $14.7 million. The significant items in the decrease in operating assets and liabilities include a decrease in deferred revenue of $24.9 million due to amortization of the up-front payment related to the Celgene collaboration, a decrease in accounts payable of $2.2

million and a decrease in prepaid expenses and other assets of $0.3 million offset by an increase in accrued expenses and other liabilities of $10.0 million and an increase in deferred rent of $2.0 million.

The net cash provided by operating activities was $43.5 million for the year ended December 31, 2013 and primarily consisted of a net loss of $25.3 million adjusted for non-cash items including stock-based compensation of $6.5 million, depreciation and amortization of $0.9 million, re-measurement of warrants of $0.4 million and a net increase in operating assets and liabilities of $60.9 million. The significant items in the increase in operating assets and liabilities include an increase in deferred revenue of $54.9 million due to the up-front payment related to the Celgene collaboration, an increase in deferred rent of $7.4 million related to leasehold improvements at our new corporate headquarters, and an increase in accounts payable of $2.1 million, slightly offset by an increase in prepaid expenses and other assets of $4.2 million.

Cash Flows from Investing Activities. Net cash used in investing activities for the year ended December 31, 2015 was $571.9 million and was primarily due to the purchase of $755.2 million of available-for-sale marketable securities offset by $199.2 million in proceeds from the maturities of available-for-sale marketable securities.

Net cash used in investing activities for the year ended December 31, 2014 was $157.2 million and was primarily due to the purchase of $175.0 million of available-for-sale marketable securities, purchase of fixed assets of $8.7 million and cash paid in connection with the acquisition of Pregenen of $4.7 million. The fixed asset purchases primarily consisted of leasehold improvements for the build-out of our new corporate headquarters. These decreases were partially offset by $31.0 million in proceeds from the maturities of investments.

Net cash used in investing activities for the year ended December 31, 2013 was $9.8 million and consisted primarily of purchases of property and equipment of $8.7 million and the new $1.3 million cash-collateralized irrevocable standby letter of credit on the corporate headquarters lease that we signed in June 2013. The fixed asset purchases primarily consisted of leasehold improvements at our new corporate headquarters and purchases of lab equipment for the additional lab space added during the first quarter of 2013 and lab equipment to support the start-up of the Celgene program. The new $1.3 million letter of credit, naming our landlord as beneficiary, is reduced to $1.0 million, $0.8 million, and $0.6 million upon the rent commencement date and the first and second anniversaries of the rent commencement date, respectively.

Cash Flows from Financing Activities: Net cash provided by financing activities for the year ended December 31, 2015 was $486.7 million and was primarily due to proceeds from our June 2015 common stock offering and $10.1 million proceeds from the issuance of common stock, primarily related to the exercise of stock options.

Net cash provided by financing activities for the year ended December 31, 2014 was $358.5 million and was primarily due to proceeds from our July and December 2014 common stock offerings.

Net cash provided by financing activities for the year ended December 31, 2013 was $105.6 million and was primarily due to the issuance of 6,832,352 common stock related to our IPO that closed on June 24, 2013, for total proceeds of $104.9 million, the repayment of a non-recourse note collateralized by restricted stock of $0.3 million, and proceeds from the exercise of common stock options of $0.4 million.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations at December 31, 2015.

	Total	2016	2017	2019	After

			through 2018	through 2020	2020
	(in thousands)				
150 Second Street Lease	$24,987	$3,261	$6,818	$7,234	$7,674
60 Binney Street Lease	197,948	—	31,652	38,164	128,132
Other operating leases (1)	1,316	1,189	127	—	—
License costs (2)	4,737	927	1,865	1,945	—
Sponsored research agreements	1,318	1,318	—	—	—
Total	$230,306	$6,695	$40,462	$47,343	$135,806

(1) Includes costs of our 215 First Street, Cambridge, Massachusetts office lease and the lease for our lab and office space in Seattle, Washington.

(2) License costs include annual license maintenance fee payments. We have not included annual license maintenance fees or minimum royalty payments after December 31, 2020, as we cannot estimate if they will occur.

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain development, regulatory and commercial milestones (such as the start of a clinical trial, filing of a BLA, approval by the FDA or product launch). We have not included these commitments on our balance sheet or in the table above because the achievement and timing of these milestones is not fixed and determinable. These commitments include:

- In connection with the Pregenen acquisition, we agreed to make contingent cash payments to the former equityholders of Pregenen. In accordance with accounting for business combinations guidance, these contingent cash payments are recorded as contingent consideration liabilities on our consolidated balance sheets at fair value. During the second quarter of 2015, a $1.0 million milestone was achieved, which resulted in a $1.0 million payment to the former equityholders of Pregenen during the third quarter of 2015. The aggregate remaining undiscounted amount of contingent consideration potentially payable is $134.0 million.
- Under a license agreement with Inserm-Transfert pursuant to which we license certain patents and know-how for use in adrenoleukodystrophy therapy, we will be required to make payments based upon development, regulatory and commercial milestones for any products covered by the in-licensed intellectual property. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €0.3, €0.2 and €1.6 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits. The royalty is subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.
- Under a license agreement with Institut Pasteur pursuant to which we license certain patents for use in ex vivo gene therapy, we will be required to make payments per product covered by the in-licensed intellectual property upon the achievement of development and regulatory milestones, depending on the indication and the method of treatment. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €1.5 and €2.0 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which varies slightly depending on the indication of the product. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the low single digits to mid-range double digits depending on the nature of the sublicense and stage of development. Starting in 2016, we will be required to make an annual maintenance payment, which is creditable against royalty payments on a year-by-year basis. On April 1, 2015, we amended this license agreement with Institut Pasteur, which resulted in a payment of $3.3 million (€3.0 million) that was paid during the second quarter of 2015.
- Under a license agreement with the Board of Trustees of the Leland Stanford Junior University, or Stanford, pursuant to which we license the HEK293T cell line for use in gene therapy products, we are required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits that varies with net sales. The royalty is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage that is less than one percent. We have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.
- Under a license agreement with the Massachusetts Institute of Technology, or MIT, pursuant to which we license various patents, we will be required to make a payment of $0.1 million based upon a regulatory filing milestone. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property by us or our sublicensees. The royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one percent. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the mid-single digits to low double digits. We are required to pay MIT an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.
- Under a license agreement with Research Development Foundation pursuant to which we license patents that involve lentiviral vectors, we will be required to make payments of $1.0 million based upon a regulatory milestone for each product covered by the in-licensed intellectual property. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which is reduced by half if during the ten year following first marketing approval the last valid claim within the licensed patent that covers the

licensed product expires or ends.

We enter into contracts in the normal course of business with CROs for preclinical research studies and clinical trials, research supplies and other services and products for operating purposes. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments.

On June 3, 2013, we entered into a nine-year building lease for approximately 43,600 square feet of space located at 150 Second Street, Cambridge, Massachusetts, commencing on the earlier of the substantial completion of our build-out work or January 1, 2014. This lease was amended in June 2014 to add an additional approximately 9,900 square feet. The lease originally had monthly lease payments of $0.2 million for the first 12 months, which increased to $0.3 million per month beginning in December 2014 due to the lease amendment, with annual rent escalations thereafter and provides a rent abatement of $0.2 million per month for the first six months. The total operating lease obligation of the noncancellable term of this agreement is $29.5 million. In addition, the lease provides a contribution from the landlord towards the initial build-out of the space of up to $7.8 million. We have the option to extend

this lease by an additional five years. In accordance with the lease, we entered into a cash-collateralized irrevocable standby letter of credit in the amount of $1.3 million, naming the landlord as beneficiary. This letter of credit was reduced to $0.8 million during the second quarter of 2015, which was the first anniversary of the rent commencement date, and may be further reduced to $0.6 million upon the second anniversary of the rent commencement date.

On June 29, 2015, we entered into a lease agreement for additional office space located at 215 First Street, Cambridge, Massachusetts. Under the terms of the lease, we leased approximately 15,120 square feet starting on July 13, 2015 for $0.5 million per year in base rent, which is subject to a 3% annual rent increase plus certain operating expenses and taxes. The lease will continue until the end of the 60th full calendar month following the date the landlord delivers the premises to us, and includes early termination provisions that could allow us to terminate the lease at the end of the 20th full calendar month following the delivery of the premises if we meet certain conditions specified within the lease. Under the terms of the lease, we have also leased an additional 8,075 square feet of office space in the same premises starting on January 1, 2016 for an additional $0.3 million per year in base rent, which is subject to a 3% annual rent increase plus certain operating expenses and taxes.

On September 21, 2015, we entered into a lease agreement for additional office and laboratory space located in a building under construction at 60 Binney Street, Cambridge, Massachusetts. Under the terms of the lease, starting on October 1, 2016, we will lease approximately 253,108 square feet at $72.50 per square foot per year, or $18.4 million per year in base rent, which is subject to scheduled annual rent increases of 1.75% plus certain operating expenses and taxes. We also executed a $9.2 million letter of credit upon signing the lease, which was required to be collateralized with a bank account at a financial institution in accordance with the lease agreement. The lease will continue until the end of the 120th full calendar month following April 2017 or the earlier the date we occupy the building or other conditions specified in the lease occur. Pursuant to a work letter entered into in connection with the lease, the landlord will contribute an aggregate of $42.4 million toward the cost of construction and tenant improvements for the building. The purpose of the lease is to supplement and eventually replace our current leased premises at 150 Second Street and 215 First Street in Cambridge, Massachusetts and we intend to move our corporate headquarters to 60 Binney Street in mid-2017. We have the option to extend the lease for two successive five-year terms.

We also lease approximately 7,800 square feet of office and laboratory space in Seattle, Washington, which lease expires in December 2016.

Off-Balance Sheet Arrangements

As of December 31, 2015, we did not have any off-balance sheet arrangements as defined in the rules and regulations of the SEC.

Item 7A. Quantitative and Qualitative Disclosures about Market Risks

We are exposed to market risk related to changes in interest rates. As of December 31, 2015 and 2014, we had cash, cash equivalents and marketable securities of $865.8 million and $492.0 million, respectively, primarily invested in U.S. Treasuries, U.S. government agency securities, federally insured deposits, certificates of deposit and money market funds. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase. If market interest rates were to increase immediately and uniformly by 100 basis points, or one percentage point, from levels at December 31, 2015, the net fair value of our interest-sensitive marketable securities would have resulted in a hypothetical decline of $7.6 million.

Item 8. Financial Statements and Supplementary Data

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

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a- 15(e) and 15d- 15(e) under the Securities Exchange Act of 1934, as amended (the “Exchange Act”)), as of the end of the period covered by this Annual Report on Form 10-K. Based on

such evaluation, our principal executive officer and principal financial officer have concluded that as of such date, our disclosure controls and procedures were effective.

Management's Annual Report on Internal Control Over Financial Reporting

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

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements. Under the supervision and with the participation of management, including our principal executive and financial officers, we assessed our internal control over financial reporting as of December 31, 2015, based on criteria for effective internal control over financial reporting established in Internal Control — Integrated Framework (2013), issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Our management's assessment of the effectiveness of our internal control over financial reporting included testing and evaluating the design and operating effectiveness of our internal controls. In our management's opinion, we have maintained effective internal control over financial reporting as of December 31, 2015, based on criteria established in the COSO 2013 framework.

The effectiveness of the our internal control over financial reporting as of December 31, 2015 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which is included herein.

Inherent Limitations of Internal Controls

Our management, including our Chief Executive Officer and Chief Financial Officer, does not expect that our disclosure controls and procedures or our internal controls will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the Company have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions, or the degree of compliance with the policies or procedures may deteriorate. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting during our most recent fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of

bluebird bio, Inc.

We have audited bluebird bio, Inc.'s internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). bluebird bio, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

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

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

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

In our opinion, bluebird bio, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2015, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of bluebird bio, Inc. as of December 31, 2015 and 2014, and the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2015 of bluebird bio, Inc. and our report dated February 25, 2016 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 25, 2016

Item 9B. Other Information

Our policy governing transactions in our securities by our directors, officers, and employees permits our officers, directors and certain other persons to enter into trading plans complying with Rule 10b5-1 under the Securities Exchange Act of 1934, as amended. We have been advised that certain of our officers (including Nick Leschly, Chief Executive Officer, Jeffrey Walsh, Chief Operating Officer, David Davidson, Chief Medical Officer, Jason Cole,

Senior Vice President and General Counsel and Eric Sullivan, Senior Director, Finance and Principal Accounting Officer) and certain of our directors (including Daniel Lynch and James Mandell) have entered into trading plans covering periods after the date of this annual report on Form 10-K in accordance with Rule 10b5-1 and our policy governing transactions in our securities. Generally, under these trading plans, the individual relinquishes control over the transactions once the trading plan is put into place. Accordingly, sales under these plans may occur at any time, including possibly before, simultaneously with, or immediately after significant events involving our company. We do not undertake to report Rule 10b5-1 trading plans that may be adopted by any officers or directors in the future, or to report any modifications or termination of any publicly announced trading plan, except to the extent required by law.

On February 24, 2016, Jeffrey T. Walsh was appointed our Chief Financial and Strategy Officer and principal financial officer, in each case, effective March 1, 2016. Mr. Walsh, 50, has served as our Chief Operating Officer since May 2011 (and will serve as such through February 29, 2016) and previously served as our principal financial officer from June 2013 to November 2014. Prior to becoming our Chief Operating Officer, Mr. Walsh served as chief business officer of Taligen Therapeutics, Inc. from November 2008 to February 2011. Mr. Walsh has also held senior business development, finance and operations roles at PathoGenesis Corp. (acquired by Chiron Corporation), Allscripts Healthcare Solutions Inc., EXACT Sciences Corporation and Inotek Pharmaceuticals Corp. There are no new arrangements or understandings between Mr. Walsh and us in connection with his appointment as our Chief Financial and Strategy Officer and principal financial officer.

In connection with the appointment of Mr. Walsh and effective as of March 1, 2016, James M. DeTore will no longer serve as our Chief Financial Officer and Treasurer and principal financial officer, and Mr. DeTore’s employment with us will end on March 18,

2016. In connection with the termination of Mr. DeTore's employment, he is entitled to certain severance benefits pursuant to the terms of an employment agreement, dated October 20, 2014, between us and Mr. DeTore. Mr. DeTore's departure did not result from any disagreement regarding our financial reporting or accounting policies, procedures, estimates or judgments.

Also on February 24, 2016, Eric Sullivan was appointed our Vice President, Finance and Treasurer, effective March 1, 2016. Mr. Sullivan, who has served as our Senior Director of Finance since November 2013 (and will serve as such through February 29, 2016), will continue to serve as our principal accounting officer, a position he has held since March 2014. There are no new arrangements or understandings between Mr. Sullivan and us in connection with his appointment as our Vice President, Finance and Treasurer.

PART III

Item 10. Directors, Executive Officers, and Corporate Governance

Incorporated by reference from the information in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 11. Executive Compensation

Incorporated by reference from the information in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

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

Incorporated by reference from the information in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 13. Certain Relationships and Related Transactions and Director Independence

Incorporated by reference from the information in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 14. Principal Accountant Fees and Services

Incorporated by reference from the information in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

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PART IV

Item 15. Exhibits, Financial Statements and Schedules

(a)(1) Financial Statements.

The response to this portion of Item 15 is set forth under Item 8 above.

(a)(2) Financial Statement Schedules.

All schedules have been omitted because they are not required or because the required information is given in the Consolidated Financial Statements or Notes thereto set forth under Item 8 above.

(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.

bluebird bio, Inc.

Index to consolidated financial statements

Report of independent registered public accounting firm

The Board of Directors and Stockholders of

bluebird bio, Inc.

We have audited the accompanying consolidated balance sheets of bluebird bio, Inc. as of December 31, 2015 and 2014, and the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2015. 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. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as 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 bluebird bio, Inc. at December 31, 2015 and 2014, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), bluebird bio, Inc.'s internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 25, 2016 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 25, 2016

bluebird bio, Inc.

Consolidated Balance Sheets

(in thousands, except per share data)

	December 31,	
	2015	2014
Assets		
Current assets:		
Cash and cash equivalents	$164,269	$347,845
Marketable securities	353,680	125,710
Prepaid expenses and other current assets	6,016	6,434
Total current assets	523,965	479,989
Marketable securities	347,814	18,448
Property and equipment, net	82,614	15,740
Intangible assets, net	24,456	28,219
Goodwill	13,128	13,128
Restricted cash and other non-current assets	10,360	1,215
Total assets	$1,002,337	$556,739
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$6,334	$2,954
Accrued expenses and other current liabilities	28,145	14,649
Deferred revenue, current portion	5,889	25,375
Total current liabilities	40,368	42,978
Deferred rent, net of current portion	8,294	8,674
Deferred revenue, net of current portion	35,959	5,302
Contingent consideration, net of current portion	5,082	6,321
Construction financing lease obligation	61,901	—
Other non-current liabilities	237	2,207
Total liabilities	151,841	65,482
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Preferred stock, $0.01 par value, 5,000 shares authorized; 0 shares issued and outstanding at December 31, 2015 and December 31, 2014	—	—
Common stock, $0.01 par value, 125,000 shares authorized; 36,894 and 32,340 shares issued and outstanding at December 31, 2015 and December 31, 2014, respectively	369	323
Additional paid-in capital	1,166,585	638,389
Accumulated other comprehensive loss	(2,291)	(71)
Accumulated deficit	(314,167)	(147,384)
Total stockholders' equity	850,496	491,257
Total liabilities and stockholders' equity	$1,002,337	$556,739

See accompanying notes to consolidated financial statements.

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bluebird bio, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except per share data)

	Year ended December 31,		
	2015	2014	2013
Revenue:			
Collaboration revenue	$14,079	$25,031	$19,792
Research and license fees	—	390	389
Total revenue	14,079	25,421	20,181
Operating expenses:			
Research and development	134,038	62,574	31,002
General and administrative	46,209	23,227	14,126
Change in fair value of contingent consideration	2,869	246	—
Total operating expenses	183,116	86,047	45,128
Loss from operations	(169,037)	(60,626)	(24,947)
Other income (expense), net:			
Interest income, net	1,591	152	29
Other income (expense), net	723	(32)	(403)
Total other income (expense), net	2,314	120	(374)
Loss before income taxes	(166,723)	(60,506)	(25,321)
Income tax (expense) benefit	(60)	11,797	—
Net loss	$(166,783)	$(48,709)	$(25,321)
Net loss per share - basic and diluted	$(4.81)	$(1.83)	$(2.02)
Weighted-average number of common shares used in computing net loss per share - basic and diluted	34,669	26,546	12,555
Other comprehensive income (loss):			
Unrealized loss on available-for-sale securities, net of tax	(2,220)	(71)	—
Total other comprehensive loss	(2,220)	(71)	—
Comprehensive loss	$(169,003)	$(48,780)	$(25,321)

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)

(in thousands)

	Series A-1 convertible preferred stock		Series A-2 convertible preferred stock		Series B convertible preferred stock		Series C convertible preferred stock		Series D convertible preferred stock	
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount
Balance at December 31, 2012	—	$ —	22,304	$7,137	115,204	$40,321	39,943	$12,382	120,409	$60,000
Vesting of restricted stock issued in exchange for nonrecourse note	—	—	—	—	—	—	—	—	—	—
Vesting of restricted stock	—	—	—	—	—	—	—	—	—	—
Proceeds from IPO, net of closing costs of $11,229	—	—	—	—	—	—	—	—	—	—
Conversion of convertible preferred stock into common stock	—	—	(22,304)	(7,137)	(115,204)	(40,321)	(39,943)	(12,382)	(120,409)	(60,000)
Reclassification of warrants to purchase preferred stock to stockholders' equity	—	—	—	—	—	—	—	—	—	—
Repayment of nonrecourse note	—	—	—	—	—	—	—	—	—	—
Exercise of common stock	—	—	—	—	—	—	—	—	—	—

warrants										
Exercise of stock options	—	—	—	—	—	—	—	—	—	—
Stock-based compensation										
Net loss	—	—	—	—	—	—	—	—	—	—
Balance at December 31, 2013	—	$ —	—	$—	—	$—	—	$—	—	$—

	Series A-1 convertible preferred stock		Common stock		Additional paid-in	Accumulated other comprehensive income	Accumulated	Total stockholders' equity
	Shares	Amount	Shares	Amount	capital	(loss)	deficit	(deficit)
Balance at December 31, 2012	12,981	$2,337	309	$ 3	$15,267	$ —	$ (73,354)	$ (55,747)
Vesting of restricted stock issued in exchange for nonrecourse note	—	—	41	—	—	—	—	—
Vesting of restricted stock	—	—	45	—	—	—	—	—
Proceeds from IPO, net of closing costs of $11,229	—	—	6,832	69	104,852	—	—	104,921
Conversion of convertible preferred stock into common stock	(12,981)	(2,337)	16,389	164	122,014	—	—	119,841
Reclassification of warrants to purchase preferred stock to stockholders' equity	—	—	—	—	655	—	—	655
Repayment of nonrecourse note	—	—	—	—	344	—	—	344
Exercise of common stock warrants	—	—	102	1	(1)	—	—	—
Exercise of stock options	—	—	222	2	481	—	—	483
Stock-based compensation					6,491	—	—	6,491
Net loss	—	—	—	—	—	—	(25,321)	(25,321)
Balance at December 31, 2013	—	$—	23,940	$ 239	$250,103	$ —	$ (98,675)	$ 151,667

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bluebird bio, Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)

(in thousands)

	Series A-1 convertible preferred stock		Series A-2 convertible preferred stock		Series B convertible preferred stock		Series C convertible preferred stock		Series D convertible preferred stock	
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount
Balance at December 31, 2013	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —
Vesting of restricted stock issued in exchange for nonrecourse note	—	—	—	—	—	—	—	—	—	—
Issuance of common stock upon public offering, net of issuance costs of $23,295	—	—	—	—	—	—	—	—	—	—
Issuance of common stock in connection with acquisition	—	—	—	—	—	—	—	—	—	—
Exercise of common stock warrants	—	—	—	—	—	—	—	—	—	—
Exercise of stock options	—	—	—	—	—	—	—	—	—	—
Issuance of common stock in exchange for consulting services to non-employees	—	—	—	—	—	—	—	—	—	—
Stock-based compensation	—	—	—	—	—	—	—	—	—	—
Unrealized loss on available-for-sale securities, net of tax	—	—	—	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	—	—	—	—	—
Balance at December 31, 2014	—	$ —	—	$ —	—	$ —	—	$ —	—	$ —

	Series A-1 convertible preferred stock		Common stock		Additional paid-in	Accumulated other comprehensive income	Accumulated	Total stockholders' equity
	Shares	Amount	Shares	Amount	capital	(loss)	deficit	(deficit)
Balance at December 31, 2013	—	$ —	23,940	$ 239	$ 250,103	$ —	$ (98,675)	$ 151,667
Vesting of restricted stock issued	—	—	69	1	(1)	—	—	—

in exchange for nonrecourse note						
Issuance of common stock upon						
public offering, net of issuance						
costs of $23,295	—	—	6,498	65	352,977	—