bluebird bio, Inc.
Form 10-K
February 22, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number: 001-35966

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 No

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 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.

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 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

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, 2016, the last business day of the registrant's most recently completed second quarter, was $1,586,834,900.

As of February 17, 2017, there were 40,844,757 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 2017 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.

Table of Contents

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 for our product candidates;
- 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 diseases and cancer. 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. Our clinical programs in severe genetic diseases include our LentiGlobin® product candidate to treat transfusion-dependent -thalassemia, or TDT, and to treat severe sickle cell disease, or severe SCD, and our Lenti-D™ product candidate to treat cerebral adrenoleukodystrophy, or CALD. Our programs in oncology 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. bb2121, our lead product candidate in oncology, is a CAR T cell product candidate for the treatment of 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 four clinical studies of our LentiGlobin product candidate: a Phase I/II study in the United States, Australia, and Thailand for the treatment of subjects with TDT, called the Northstar Study (HGB-204); a multi-site, international, Phase III study for the treatment of subjects with TDT and non-$^{0}/^{0}$ genotypes, called the Northstar-2 Study (HGB-207); a single-center Phase I/II study in France for the treatment of subjects who with TDT or with severe SCD (HGB-205); and a multi-site Phase I study in the United States for the treatment of subjects with severe SCD (HGB-206). 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 and for the treatment of certain patients with severe SCD. The FDA has granted Breakthrough Therapy designation to our LentiGlobin product candidate for the treatment of transfusion-dependent patients with -thalassemia major. The EMA has granted access to its Priority Medicines (PRIME) scheme for our LentiGlobin product candidate for the treatment of TDT.

We are conducting a multi-site, international, Phase II/III clinical study of our Lenti-D™ product candidate, called the Starbeam Study (ALD-102), for the treatment of subjects with CALD, a rare, hereditary neurological disorder that is often fatal. Our Lenti-D product candidate has been granted Orphan Drug status by the FDA and the EMA for the treatment of adrenoleukodystrophy.

We are conducting a multi-site Phase I clinical study in the United States of our bb2121 product candidate for the treatment of subjects with relapsed/refractory multiple myeloma (CRB-401). bb2121 is the lead product candidate arising from our multi-year collaboration with Celgene Corporation, or Celgene, for the discovery, development and commercialization of CAR T cell therapies targeting B-cell maturation antigen, or BCMA. We have exclusively licensed to Celgene the right to develop and commercialize our bb2121 product candidate, and we may exercise our option to co-develop and co-promote this product candidate in the United States. The FDA has granted Orphan Drug status to bb2121 for the treatment of patients with relapsed/refractory multiple myeloma.

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 hematopoietic stem cells, or HSCs, in the case of our LentiGlobin and Lenti-D product candidates, or the patient's own isolated white blood cells which include T cells, in the case of our bb2121 product candidate. 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 and T cells. 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 that are derived from HSCs, such as microglia (useful for CALD), red blood cells (useful for TDT and SCD) or other cells, or from T cells (useful for cancer and immunology).

We also have discovery research programs utilizing our cell signaling technology and gene editing technology platform across our pipeline. For instance, we are exploring applications of our CAR and TCR T cell technologies in combination with novel proteins based on synthetic biology. These technologies may potentially allow our future T cell-based product candidates to detect the tumor microenvironment or, in the case of future CAR T cell product candidates, to be regulated by small molecules. In addition, 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 edit or insert genetic components to potentially treat a variety of diseases.

Our gene therapy platform and proprietary lentiviral vectors

Our gene therapy product candidates for severe genetic diseases and in cancer 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 in severe genetic diseases (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 TDT and severe 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 severe genetic diseases

The delivery of a gene therapy product in HSCs for the treatment of severe genetic diseases 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. A sample of HSCs is extracted from the patient 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 isolated and collected from the patient's blood. HSCs may also be extracted directly from the patient's bone marrow, particularly as in the treatment of severe SCD.
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 oncology

The delivery of modified T cell products in oncology requires several steps that are similar to our therapeutic approach in severe genetic diseases with HSCs. Importantly, our approach seeks to leverage cell transplant procedures and infrastructure already widely used in the clinic for autologous and 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 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.

3

Our product candidate pipeline

We are developing our LentiGlobin product candidate to treat patients with TDT and severe SCD. We are conducting four clinical studies of our LentiGlobin product candidate: a Phase I/II study in the United States, Australia, and Thailand to evaluate its safety and efficacy in the treatment of subjects with TDT, called the Northstar Study (HGB-204); a multi-site, international, Phase III study to evaluate its safety and efficacy in the treatment of subjects with TDT and a non-$^{0}/^{0}$ genotype, called the Northstar-2 Study (HGB-207); a single-center Phase I/II study in France to evaluate its safety and efficacy in the treatment of subjects with TDT or with severe SCD (HGB-205); and a multi-site Phase I study in the United States to evaluate its safety and efficacy in the treatment of subjects with severe SCD (HGB-206). In addition, in 2017 we intend to initiate our planned Phase III study of our LentiGlobin product candidate for the treatment of subjects with TDT and a $^{0}/^{0}$ genotype, called the Northstar-3 Study (HGB-212).

We are developing our Lenti-D product candidate to treat patients with CALD. We are 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 (ALD-102), to examine the safety and efficacy of our Lenti-D product candidate in subjects with CALD.

We are also pursuing opportunities to apply our gene therapy platform technologies in cancer by genetically modifying a patient's own T cells to target and destroy cancer cells. Our collaboration with Celgene focuses on CAR T cell product candidates directed against BCMA, a protein expressed on the surface of multiple myeloma cells, plasma cells and some mature B cells. We are conducting a multi-site Phase I clinical study in the United States to evaluate the safety and efficacy of our bb2121 product candidate, the lead product candidate from this collaboration, in the treatment of subjects with relapsed/refractory multiple myeloma (CRB-401). We have exclusively licensed to Celgene the right to develop and commercialize our bb2121 product candidate, while we have retained an option to co-develop and co-promote this product candidate in the United States. In addition, we anticipate initiating in 2017 a Phase I clinical study in the United States to evaluate the safety and efficacy of the next anti-BCMA CAR T cell product candidate arising from our collaboration with Celgene. We are also collaborating with Kite Pharma, Inc. in the research and development of second-generation TCR product candidates directed against an antigen relating to certain cancers associated with the human papilloma virus, and with Medigene AG, through its subsidiary Medigene Immunotherapies GmbH, in the research and development of TCR product candidates directed against up to four antigens for the treatment of cancer indications.

Our LentiGlobin product candidate opportunity

-thalassemia

Overview

-thalassemia is a rare hereditary blood disorder caused by a mutation in the -globin gene resulting in the production of defective red blood cells, or RBCs. Genetic mutations cause the absence or reduced production of the beta chains of hemoglobin, or -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 -globin. Genetic mutations that impair the production of -globin can lead to a relative excess of a-globin, leading to premature death of RBCs. The clinical implications of the a-globin/ -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 a range of multi-systemic complications, including but not limited to splenomegaly, marrow expansion, bone deformities, and iron overload in major organs.

The clinical course of -thalassemia correlates with the degree of globin chain imbalance. Nearly 200 different mutations have been described in patients with -thalassemia. The clinical presentation varies widely, dependent largely upon the type of inherited mutation. Mutations can be categorized as those that result in no functional -globin production (^{0}) and those that result in decreased functional -globin production^{+}(). 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 ^{0}/ ^{0} genotypes as well as many patients with other genotypes resulting in abnormal -globin production, such as th^{0}/$^{+}$ and $^{+}$/$^{+}$ genotypes. Affected patients produce as little as one to seven g/dL of hemoglobin (in contrast, a normal adult produces 12-18 g/dL of hemoglobin). Hemoglobin E (^{E}), which is another -globin mutation and is usually asymptomatic, can also result in TDT when paired with ^{0} or $^{+}$ mutations.

Limitations of current treatment options

In geographies where treatment is available, patients with TDT receive chronic blood transfusion regimens. These regimens consist of regular infusions with units of packed RBC, or pRBC, usually every three to five weeks, which are intended to maintain hemoglobin levels and control 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 significant morbidity and mortality through iron-

associated heart and liver toxicity. To help prevent iron overload-associated risks and resulting complications, 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 -thalassemia today is allogeneic HSCT. However, complications of allogeneic HSCT include a risk of engraftment failure in unrelated human-leukocyte-antigen, or HLA, matched patients, a risk of life-threatening infection, and a 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 only a fraction 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.

Sickle cell disease

Overview

Sickle cell disease, or SCD, is a hereditary blood disorder resulting from a mutation in the -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 small blood vessels of the body), cumulative damage to multiple organs, 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.

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 SCD and is recommended for patients with recurrent episodes of acute pain or specific frequencies of painful crises. Not all SCD patients respond to hydroxyurea however, or are able to tolerate the cytotoxic effect of reduced white blood cell and platelet counts. A significant number of patients with severe 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 sickle hemoglobin below 30% to 50%, which decreases sickling of RBCs, reduces the risk of recurrent stroke, and decreases the incidence of associated co-morbidities. 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 severe 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 only a fraction of eligible patients undergo transplant. In light of these factors, we believe that severe 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 -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 -globin protein in patients with TDT and severe SCD, while also providing anti-sickling properties in the context of severe SCD. We refer to the cells that have undergone our ex vivo manufacturing process resulting in genetically modified HSCs as the final LentiGlobin drug product, or our LentiGlobin product candidate.

We are conducting three clinical studies of our LentiGlobin product candidate to evaluate its safety and efficacy in the treatment of subjects with TDT. In December 2013, we announced that the first subject with TDT had been treated in our HGB-205 study, which also includes the enrollment of subjects with severe SCD. In March 2014, we announced that the first subject with TDT had been treated in our Northstar Study (HGB-204). We presented interim results from both our Northstar Study and our HGB-205 study at the American Society of Hematology Annual Meeting in December 2016. We also announced in December 2016 that the first subject had been treated in our Northstar-2 Study (HGB-207), which evaluates the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with TDT and non-$^{0}/^{0}$ genotypes. In addition, we intend to initiate in 2017 our planned Phase III study of our LentiGlobin product candidate for the treatment of subjects with TDT and a $^{0}/^{0}$ genotype, called the Northstar-3 Study (HGB-212). In October 2014, we announced that the first subject with severe SCD had been treated in our HGB-205 study. We are also conducting our HGB-206 study to evaluate the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with severe SCD. In 2016, we amended the protocol of our HGB-206 study to expand enrollment and to incorporate several process changes, including our updated drug product manufacturing process. In February 2017, we announced that the first subject has been treated under this amended protocol. We will be using our updated drug product manufacturing process with the objective of increasing the vector copy number and the percentage of transduced cells in the LentiGlobin drug product in our ongoing Northstar-2 Study, our HGB-206 study under the amended protocol, and our planned Northstar-3 Study.

If successful, we believe that data from the ongoing Northstar Study and Northstar-2 Study could form the basis for a biologics licensing application, or BLA, submission for our LentiGlobin product candidate in the United States for the treatment of patients with TDT and non-$^{0}/^{0}$ genotypes. In addition, if successful, we believe the data from our planned Northstar-3 Study, together with data from our ongoing Northstar Study, Northstar-2 Study and HGB-205 study, could be sufficient to form the basis for a BLA supplement submission for our LentiGlobin product candidate for the treatment of patients with TDT and a $^{0}/^{0}$ genotype.

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 and for the treatment of certain patients with severe SCD. The FDA has 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 that it is possible to seek conditional approval for LentiGlobin for the treatment of TDT on the basis of the totality of the clinical data from our ongoing Northstar Study and HGB-205 study, assuming these studies demonstrate acceptable efficacy and safety, respectively, and in particular a reduction in transfusion requirements. We believe that conversion to full approval would be subject to the successful completion of our ongoing Northstar-2 Study and our planned Northstar-3 Study, supportive long-term follow-up data and "real-world" 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. In addition, the EMA has granted access to its Priority Medicines (PRIME) scheme for our LentiGlobin product candidate in the treatment of TDT.

Clinical development of our LentiGlobin product candidate

The Northstar Study (HGB-204) – Phase I/II clinical study in subjects with TDT

Our 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.

Eighteen adults and adolescents have been enrolled in the study. To be eligible for enrollment in this study, subjects were 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 were also eligible for allogeneic HSCT. In September 2016, we announced that our Northstar Study has been fully enrolled.

Efficacy will be evaluated primarily by the production of ≥2.0 g/dL of hemoglobin A containing $^{A\text{-}T87Q}$-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 ≥2.0 g/dL of hemoglobin A containing $^{A\text{-}T87Q}$-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.

The HGB-205 study – Phase I/II clinical study in subjects with TDT or with severe SCD

Our HGB-205 study is a single-dose, open-label, non-randomized, Phase I/II clinical study at a single site in France 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 our HGB-205 study and in October 2014 we announced that the first subject with severe SCD had been treated in our 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.

The primary objective of our HGB-205 study is to determine the safety, tolerability and success of engraftment of the LentiGlobin drug product. The secondary objectives of the study are to quantify gene transfer efficiency and expression, and to measure the effects of treatment with the LentiGlobin drug product on disease-specific biological parameters and clinical events. In the case of subjects with TDT and SCD, this means the volume of pRBC transfusions, and for subjects with SCD, it also means the number of vaso-occlusive crises and acute chest syndrome events in each subject, compared with the two-year period prior to treatment.

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.

The HGB-206 study – Phase I clinical study in subjects with severe SCD

Our 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 29 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.

In October 2016, we announced that we have amended the protocol for our HGB-206 study to incorporate several changes with the goal of increasing production of anti-sickling -globin, such as increasing the percentage of transduced cells through manufacturing improvements, increasing target busulfan area under the curve, introducing a minimum period of regular blood transfusions prior to stem cell collection, and exploring an alternate HSC procurement method, with the goal of increasing transduced cell dose. Enrollment has begun under this amended protocol and in February 2017, we treated the first subject under this amended protocol.

The Northstar-2 Study (HGB-207) – Phase III study in subjects with TDT and a non-$^{0}/_{0}$ genotype

Our Northstar-2 Study is an ongoing single-dose, open-label, non-randomized, international, multi-site Phase III clinical study to evaluate the safety and efficacy of the LentiGlobin product candidate to treat subjects with TDT and a non-$^{0}/_{0}$ genotype.

Approximately 23 subjects will be enrolled in the study, consisting of at least 15 adolescent and adult subjects between 12 and 50 years of age at enrollment, and at least eight pediatric subjects less than 12 years of age at enrollment. To be enrolled, subjects with TDT and a non-$^{0}/^{0}$ genotype must have received at least 100 mL/kg/year of pRBCs per year for the past two years. All subjects must be eligible for allogeneic HSCT, but without a matched sibling allogeneic HSCT donor.

The primary endpoint of this study is the proportion of treated subjects who achieve transfusion independence, defined as hemoglobin levels ≥9.0 g/dL without any pRBC transfusions for a continuous period of at least 12 months at any time during the study after treatment. The secondary endpoints of this study are to quantify gene transfer efficiency and expression, and to measure the effects of treatment with the LentiGlobin drug product on transfusion requirements post-transplant and clinical events. Each subject will remain on study for approximately 24 months from time of consent.

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 in our Northstar-2 Study will be treated with our LentiGlobin product candidate manufactured using our updated drug product manufacturing process with the objective of increasing the vector copy number and the percentage of transduced cells. In December 2016, we announced the first subject had received treatment with our LentiGlobin product candidate.

The planned Northstar-3 Study (HGB-212) – Phase III Study for TDT in subjects with TDT and a$^{0}/^{0}$ genotype

We have discussed with the FDA and the EMA the design of our planned international, multi-site Phase III study of our LentiGlobin product candidate for subjects with TDT and a $^{0}/^{0}$ genotype, called the Northstar-3 Study (HGB-212), which we expect to enroll up to 15 adult, adolescent, and pediatric subjects. We anticipate that the primary endpoint of our planned Northstar-3 Study will be transfusion reduction, which is defined as a demonstration of a reduction in the volume of pRBC transfusion requirements in the post-treatment time period of months 12 to 24, as compared to the average annual transfusion requirements in the 24 months prior to enrollment. We intend to initiate this study in 2017.

Interim clinical data in subjects with TDT – The Northstar Study and the HGB-205 study

Interim clinical data from the Northstar Study

In December 2016, we presented interim clinical data from our Northstar Study at the Annual Meeting of the American Society of Hematology, or ASH. All data presented at ASH Annual Meeting and summarized below from our Northstar Study are as of the data cut-off date of September 16, 2016. As of the data cut-off date, ten subjects with non-$^{0}/_{0}$ genotypes and eight subjects with $^{0}/_{0}$ genotypes had undergone infusion with LentiGlobin drug product in our Northstar Study. The median follow-up period was 17 months (with a range of 6.3 to 29.8 months). Two subjects had completed the two-year primary analysis period. Below is a table summarizing the interim clinical data from our Northstar Study presented at the ASH Annual Meeting.

	Genotype $^{0}/_{0}$ genotypes	Non-$^{0}/_{0}$ genotypes
	(n=8)	(n=10)
Genotype	8	10
$^{E}/_{0}$	–	6
Other ($^{+}/_{0}$, $^{+}/_{+}$, $^{x}/_{0}$)	–	4
Age at the start of regular transfusions	0 (0 – 7)	6 (0 – 26)
Median (range) (years)		
Age at enrollment	23 (12 – 35)	19.5 (16 – 34)
Median (range) (years)		
Transfusion requirements prior to study entry	184.9 (128.7 – 261.3)	146.3 (117.0 – 234.5)
Annualized median (range) (mL/kg/year)		
Splenectomy	3	3
LentiGlobin drug product VCN [1]	0.7 (0.3 – 1.5)	0.8 (0.3 – 1.1)
Median (range) (c/dg)		
LentiGlobin drug product cell dose	11.0 (6.1 – 18.1)	7.1 (5.2 – 13.0)
Median (range) CD34+ cell count (x10^{6}/kg)		
In vivo VCN at six months of follow-up	0.3 (0.1 – 1.0)	0.4 (0.1 – 0.9)
Median (range) (c/dg)		

[1] VCN is a measurement of the mean number of viral vectors in a population of cells, or vector copies per diploid genome. In the case of LentiGlobin drug product VCN, the measurement is prior to infusion of the study subject. If more than one lot of drug product was manufactured for a subject, the VCN of each drug product lot was quantified and the cell count is combined.

All five subjects with non-$^{0/0}$ genotypes that had at least twelve months of follow-up have been free from the need for transfusions, as of the data cut-off date. The median $^{A\text{-}T87Q}$ production for these five subjects was 11.7 g/dL, with a range of 9.5 to 12.5 g/dL. At the last follow-up, the median total hemoglobin of all ten subjects with non-$^{0/0}$ genotypes was 10.3 g/dL, with a range of 7.2 to 12.5 g/dL. The median follow up for these ten subjects was 14.7 months, ranging from 6.3 to 29.8 months. Subjects with a $^{0/0}$ genotype and at least twelve months of follow-up had a median reduction in annualized transfusion volume of 63% (ranging from 47 to 78%), and median reduction in annualized transfusion frequency of 65% (ranging from 31 to 81%), calculated based on their transfusion requirements from month 6 to the data cut-off date. The median follow-up for the eight subjects with a $^{0/0}$ genotype was 17.3 months, ranging from 6.7 to 25.4 months. Hemoglobin fractions at month 12 showed consistent production of $^{A\text{-}T87Q}$ across genotypes in subjects with at least 12 months of follow-up.

A correlation between VCN and $^{A\text{-}T87Q}$ production was observed as of the data cut-off date. In our Northstar Study, the safety profile of 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 the data cut-off date.

It should be noted that these data presented above are current as of the data cut-off date, are preliminary in nature and our 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 in subjects with TDT, including this study, our ongoing HGB-205 study, our Northstar-2 Study, or our planned Northstar-3 Study. It is possible that subjects for whom transfusion support has been reduced or eliminated may receive transfusion support in the future.

Interim clinical data from the HGB-205 study

In December 2016, we presented interim clinical data from our HGB-205 study in subjects with TDT at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below from our HGB-205 study are as of the data cut-off date of

September 9, 2016. As of the data cut-off date, four subjects with TDT had undergone infusion with LentiGlobin drug product in our HGB-205 study. The subjects with TDT had between 11.6 and 33.5 months of follow-up. Three subjects with TDT and the $^{0}/_{E}$ genotype have remained free of transfusions since shortly after infusion with the LentiGlobin drug product. As of the data cut-off date, these three subjects have been free from the need for transfusions for 33.1, 29.9 and 11.5 months, respectively. The subject with TDT and homozygosity for the severe $^{+}$ mutation IVS1-110 had been free of transfusions for 11.6 months (since approximately 3 months after receiving treatment with the LentiGlobin drug product). In these subjects with TDT, treatment with our LentiGlobin product candidate has been well tolerated, with no drug product-related adverse events as of the data cut-off date. Below is a table summarizing the interim data from our HGB-205 study in subjects with TDT that were presented at the ASH Annual Meeting.

	TDT			
Subject	1201	1202	1203	1206
Age at enrollment	18	16	19	17
(years)				
Genotype	$^{0}/_{E}$	$^{0}/_{E}$	homozygous	$^{0}/_{E}$
			IVS1 nt 110 G>A	
Transfusion requirements prior to study entry [1]	139	188	176	197
(mL/kg/year)				
LentiGlobin drug product VCN [2]	1.5	2.1	0.8	1.1
(c/dg)				
LentiGlobin drug product cell dose	8.9	13.6	8.8	12.0
CD34+ cell count (x10^{6}/kg)				
Hemoglobin A^{T87Q} / Total hemoglobin	7.7 / 10.9	10.1 / 13.5	6.7 / 8.3	8.6 / 11.3
(g/dL)				
Busulfan area under the curve	4,967	5,212	4,670	4,930
Median (range) (μM/min)				
Follow up	33.5	30.3	14.6	11.6
(months)				

[1] Mean pRBC requirement per year, over the two years prior to consent.

[2] VCN is a measurement of the mean number of viral vectors in a population of cells, or vector copies per diploid genome. In the case of LentiGlobin drug product VCN, the measurement is prior to infusion of the study subject. If more than one lot of drug product was manufactured for a subject, the VCN of each drug product lot was quantified and the cell count is combined.

It should be noted that these data presented above are current as of the data cut-off date, are preliminary in nature and our 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 in subjects with TDT, including this study, our ongoing Northstar Study, our Northstar-2 Study, or our planned Northstar-3 Study. It is possible that subjects for whom transfusion support has been reduced or eliminated may receive transfusion support in the future. Furthermore, the LentiGlobin drug product used for the HGB-205 study is manufactured at the clinical trial site in Paris, and is not manufactured at our third-party manufacturing locations, and does not use our updated drug product manufacturing process that is being utilized in our Northstar-2 Study.

Interim clinical data in subjects with severe SCD – The HGB-205 study and the HGB-206 study

In December 2016, we presented interim clinical data from our HGB-205 study regarding a subject with severe SCD at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below from our HGB-205 study are as of the data cut-off date of September 9, 2016. As of the data cut-off date, one subject with severe SCD had undergone infusion with LentiGlobin drug product in our HGB-205 study, with 22.9 months of follow up. At the 21-month post-infusion follow up for the subject with severe SCD, the proportion of anti-sickling hemoglobin accounted for over 48 percent of all hemoglobin production, which was above the 30 percent threshold expected to potentially achieve a disease-modifying clinical effect. Prior to infusion, this subject required chronic blood transfusions to reduce the occurrence of vaso-occlusive crises. Since infusion with LentiGlobin drug product, this subject has not received a pRBC transfusion for more than 18 months. Since infusion and as of the data cut-off date, this subject had no hospitalizations or acute SCD-related events. In this subject with severe SCD, treatment with our LentiGlobin product candidate has been well tolerated, with no drug product-related adverse events as of the data cut-off date.

Also at the ASH Annual Meeting in December 2016, we presented preliminary clinical data from our HGB-206 study in subjects with severe SCD. All data presented at the ASH Annual Meeting and summarized below from our HGB-206 study are as of the data cut-off date of November 9, 2016. As of the data cut-off date, seven subjects with severe SCD have been infused with LentiGlobin

drug product under the original study protocol for our HGB-206 study. One subject experienced a steady increase in hemoglobin levels and is producing 2.0 g/dL HbA^{T87Q} with 22.8% overall anti-sickling hemoglobin (HbA^{T87Q} + HbF), even after a substantial drop in VCN measured in the drug product and the in vivo measurement taken from peripheral blood at latest follow up (from 0.9 c/dg to 0.24 c/dg at nine months follow up). As of the data cutoff, this was the only subject in our HGB-206 study who received chronic transfusions prior to receiving LentiGlobin drug product. At last follow up, all treated subjects were producing measureable HbA^{T87Q}, with a range of 0.1 to 2.0 g/dL HbA^{T87Q}. The safety profile in the infused subjects in our HGB-206 study is consistent with autologous transplantation. As of the data cut-off date, there were ten grade 3 bone marrow harvest-related adverse events that were reported in three subjects, including one severe adverse event reported for pain/ prolonged hospitalization. Six subjects experienced at least one severe adverse event post-infusion. There were no drug product-related adverse events reported as of the data cut-off date.

Below is a table summarizing the interim clinical data in subjects with severe SCD from our HGB-205 study and our HGB-206 study that were presented at the ASH Annual Meeting, and the data summarized below are as of their respective data cut-off dates. All eight subjects have a history of severe SCD in the two years prior to enrollment, despite hydroxyurea therapy. Among these eight subjects, two had a history of recurrent vaso-occlusive crises, two had a history of stroke, six had a history of acute chest syndrome, and two had regular pRBC transfusions prior to treatment with the LentiGlobin drug product.

	HGB-205	HGB-206
	(n=1)	(n=7)
Age at enrollment	13	26 (18 – 42)
Median (range) (years)		
Bone marrow harvests	2	2 (1 – 4)
Target daily busulfan area under the curve	4,841 (actual)	5,000 (4,400 – 5,400)
Median (range) (μM/min)		
LentiGlobin drug product VCN [1]	1.0, 1.2	0.6 (0.3 – 1.3)
Median (range) (c/dg)		
LentiGlobin drug product cell dose	5.6	2.1 (1.6 – 5.1)
Median (range) CD34+ cell count ($x10^6$/kg)		
Follow up	21	11.5 (8.1 – 17.1)
Median (range) (Months)		

[1] VCN is a measurement of the mean number of viral vectors in a population of cells, or vector copies per diploid genome. In the case of LentiGlobin drug product VCN, the measurement is prior to infusion of the study subject. If more than one lot of drug product was manufactured for a subject, the VCN of each drug product lot was quantified and the cell count is combined.

It should be noted that these data presented above are current as of the respective data cut-off dates, are preliminary in nature and our HGB-205 and HGB-206 studies are 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 in subjects with severe SCD, including these two ongoing studies. It is possible that subjects for whom complications of severe SCD have been reduced or eliminated may experience complications of severe SCD in the future. Furthermore, the LentiGlobin drug product used in the HGB-205 study and in the HGB-206 study under the original protocol and presented above did not utilize our updated drug product manufacturing process that is being utilized under the amended protocol for the HGB-206 study. In addition, the LentiGlobin drug product used for the HGB-205 study is manufactured at the clinical trial site in Paris, and is not manufactured at our third-party manufacturing locations.

Our Lenti-D product candidate opportunity

Adrenoleukodystrophy

Adrenoleukodystrophy is a rare X-linked, metabolic disorder caused by mutations in the ABCD1 gene which results in a deficiency in adrenoleukodystrophy protein, or ALDP and subsequent accumulation of very long-chain fatty acids, or VLCFA. VLCFA accumulation occurs in plasma and all tissue types, but primarily affects the adrenal cortex and white matter of the brain and spinal cord, leading to a range of clinical outcomes. The most severe form of ALD, the inflammatory cerebral phenotype, which we refer to as CALD, involves a progressive destruction of myelin, the protective sheath of the nerve cells in the brain that are responsible for thinking and muscle control. Symptoms of CALD usually occur in early childhood and progress rapidly if untreated, leading to severe loss of neurological function and eventual death in most patients. We estimate that a significant proportion of males with ALD will develop CALD.

Limitations of current treatment options

There is a clear unmet medical need for patients with CALD. Currently, the only effective treatment option 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 is reserved for patients in the earliest stages of cerebral 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 or partially matched related or unrelated donor cells including umbilical cord blood cells because a matched sibling donor is not available. The difficulty of finding a suitable donor is one of the primary limitations of this approach. Complications of allogeneic HSCT include a significant risk of morbidity and mortality related to graft failure, GVHD and opportunistic infections, particularly in patients who undergo non-sibling-matched allogeneic HSCT.

As the outcome of HSCT varies with clinical stage of the disease at the time of transplant, early diagnosis of CALD is important. Favorable outcomes have been observed in patients who undergo transplant in the early stages of cerebral disease. ALD can be detected at birth, allowing boys at risk for CALD to be monitored and identified prior to the onset of symptoms. In the United States, newborn screening for ALD was added to the Recommended Universal Screening Panel, or RUSP, in February 2016. The RUSP is a list of disorders that are screened at birth and recommended by the Secretary of the U.S. Department of Health and Human Services for states to screen as part of their state universal newborn screening program. Disorders are chosen based on evidence that supports the potential net benefit of screening, among other factors. A number of states in the United States have added ALD to their newborn screening programs.

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 deficient ALDP 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. In April 2016, we presented preliminary clinical data from this study at the American Academy of Neurology Annual Meeting. In December 2016, we announced that we intend to expand the Starbeam Study to enroll up to eight additional patients in an effort to enable the first manufacture of our Lenti-D product candidate in Europe, and the subsequent treatment of subjects in Europe, and to bolster our overall clinical data package for potential future regulatory filings in the United States and Europe. We plan to begin treating these additional subjects in the Starbeam Study in early 2017.

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)

CALD is a rare disease and as such, data on the natural history of the disease, as well as the efficacy and safety profile of allogeneic HSCT is limited in the scientific literature. In order to properly design 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 in comparison to the efficacy and safety data obtained from patients that received allogeneic HSCT. 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.

Starbeam Study (ALD-102) – Phase II/III clinical study in subjects with CALD

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 this study, we use the neurologic function score, or NFS, the existence and number of major functional disabilities, or MFDs, the Loes score, and evidence of gadolinium enhancement on MRI to evaluate potential subjects' eligibility for the study, and to evaluate efficacy.

The NFS is a 25-point score used to evaluate the severity of gross neurologic dysfunction by scoring 15 neurological abnormalities across multiple domains. These neurological abnormalities are listed below. 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 potential subject'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.

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)

The Loes score is a 34-point scale specifically designed to objectively measure the extent of demyelination in CALD based on brain magnetic resonance imaging, or MRI, studies. Increasing Loes scores indicate worsening disease. 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. CALD can progress rapidly and is associated with severe inflammation and disruption of the blood brain barrier which can be detected by gadolinium enhancement on MRI. Evidence of gadolinium enhancement in the brain in a MRI study, referred to by clinicians as a gadolinium positive result, is highly predictive of rapid neurologic decline. However, while pre-transplant gadolinium status is clearly correlated with rapid disease progression, the kinetics of gadolinium enhancement after clinically successful HCST are not well understood.

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. In December 2016, we amended the protocol of the Starbeam Study to enroll up to eight additional patients in an effort to enable the first manufacture of our Lenti-D product candidate in Europe and the subsequent treatment of subjects in Europe, and to bolster our overall clinical data package for potential future regulatory filings in the United States and Europe. We plan to begin treating the additional patients in early 2017.

We have defined the primary efficacy endpoint in the Starbeam Study as the proportion of subjects who have no MFDs 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.

Preliminary Clinical Data from the Starbeam Study

In April 2016, we presented preliminary clinical data from the Starbeam Study at the American Academy of Neurology (AAN) Annual Meeting. All data presented at the AAN Annual Meeting and summarized below from the Starbeam Study are as of the data cut-off date of March 31, 2016. As of the data cut-off date, 17 subjects with CALD had received Lenti-D drug product. All subjects had at least six months of follow up, with eight subjects having between 12 and 24 months of follow up.

Sixteen of 17 subjects had NFS stabilization (change of <3 points and an absolute NFS≤4). Two subjects had an increase in NFS from 0 to 1, due to the occurrence of stuttering in one patient, and episodic urinary incontinence in another patient. One patient had an early, rapidly progressive course and had an NFS of 5, reflecting deficits in speech, vision, difficulty walking and running, and episodes of urinary incontinence. Fourteen of 17 subjects had a stable Loes score (change of ≤5 points or an absolute Loes score ≤9). Sixteen of 17 had resolution of gadolinium enhancement by month six. Reemergence of diffuse contrast enhancement was seen in five subjects at month 12. Of those five subjects, the two with at least 18 months of follow up showed resolution of gadolinium enhancement at month 18.

As of the data cut-off date, the safety profile of treatment with the Lenti-D drug product appears consistent with myeloablative conditioning with one possibly drug-related serious adverse event (Grade 3 BK-mediated viral cystitis), and one possibly drug-related adverse event (Grade 1 tachycardia). Both resolved with standard measures. Integration site analyses demonstrated polyclonal reconstitution in all subjects without evidence of clonal dominance, as of the data cut-off date.

It should be noted that these data presented above are current as of the data cut-off date, are preliminary in nature and the Starbeam Study is not complete. There is limited data concerning long-term safety and efficacy following treatment with our Lenti-D product candidate. These data may not continue for these subjects or be repeated or observed in our ongoing Starbeam Study or future studies involving our Lenti-D product candidate. It is possible that subjects who exhibit NFS stabilization, a stable Loes score, or resolution of gadolinium enhancement as of the data cut-off date may ultimately progress in the future.

The ALD-103 study – Observational study

We are also conducting the ALD-103 study, an observational study of subjects with CALD treated by allogeneic HSCT. This study is ongoing and designed to collect efficacy and safety outcomes data in subjects who have undergone allogeneic HSCT in a period that is contemporaneous with the Starbeam Study. 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 in conjunction with our retrospective observational ALD-101 study and our retrospective and prospective 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 Opportunity in T Cell-Based Therapies for Cancer

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.

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 new checkpoint inhibitors such as nivolumab and pembrolizumab led to their approval by FDA (in 2015 and 2016) as treatments in multiple cancers and 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 T cell engineering process is rapid (complete in approximately 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. For instance, we are exploring applications of our CAR and TCR T cell technologies in combination with novel proteins based on synthetic biology. These technologies may potentially allow our future T cell-based product candidates to detect the tumor microenvironment or, in the case of future CAR T cell product candidates, to be regulated by small molecules. In addition, using our gene editing technology, we potentially 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 hematologic 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. BCMA is expressed on normal plasma cells, some mature B cells, and on malignant 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.

We are conducting a Phase I clinical study of our bb2121 product candidate in the United States. Our product candidate bb2121 is the lead product candidate from our multi-year collaboration with Celgene. 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. In February 2016, we exclusively licensed to Celgene the right to develop and commercialize our bb2121 product candidate. 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."

In 2017, we intend to initiate a Phase I clinical study of our bb21217 product candidate (CRB-402), a second-generation anti-BCMA CAR T cell product candidate arising from our collaboration with Celgene. Upon initiation of our planned CRB-402 study, Celgene will have the option of exclusively licensing our bb21217 product candidate, and if Celgene exercises its option, we will retain an option to co-develop and co-commercialize this product candidate.

The CRB-401 study – Phase I clinical study in subjects with relapsed/refractory multiple myeloma

Our CRB-401 study is a single-dose, open-label, non-randomized, multi-site Phase I clinical study in the United States to examine the safety and efficacy of our bb2121 product candidate in up to 50 subjects with relapsed/refractory multiple myeloma. In order to be eligible for CRB-401, subjects must have received three 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. The bb2121 drug product is produced from each subject's own blood cells, which are modified using a lentiviral vector encoding the anti-BCMA CAR. Following manufacture of the bb2121 drug product, subjects will receive one cycle of lymphodepletion of cyclophosphamide and fludarabine prior to infusion of the bb2121 drug product.

The primary endpoint of the study is the incidence of adverse events and abnormal laboratory test results, including dose-limiting toxicities. The study also seeks to assess disease-specific response criteria including: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma. The study also seeks to determine the maximally tolerated dose and recommended dose for further clinical trials.

Each subject will be followed for up to 24 months post-treatment, and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the 24-month period.

Preliminary Clinical Data from the CRB-401 Study

In December 2016, we presented preliminary clinical data from our CRB-401 study at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium, or the Triple Meeting. All data presented at the Triple Meeting and summarized below from our CRB-401 study are as of the data cut-off date of November 18, 2016. As of the data cut-off date, eleven subjects had been enrolled and dosed in four dose cohorts: 5.0 x 10^7, 15.0 x 10^7, 45.0 x 10^7 and 80 x 10^7 CAR + T cells. Subjects on study were heavily pre-treated, with a median of six prior therapies, ranging from five to 13. All eleven dosed subjects were evaluable for safety and the first nine subjects (in 5.0 x 10^7, 15.0 x 10^7, and 45.0 x 10^7 dose cohorts) have undergone their first multiple myeloma tumor restaging and were evaluable for efficacy, summarized in the table below.

	1	2	3
Cohort			
	(n=3)	(n=3)	(n=3)
CAR + T cell dose	5.0 x 10^7	15.0 x 10^7	45.0 x 10^7
Overall response rate in cohort	33%	100%	100%
Best response	PD	sCR	PR
		(time to response: 2 months)	
	SD	sCR*	PR
		(time to response: 4 months)	
	PR	VGPR*	PR

*Both subjects with a minimal residual disease assessment at month 1 were MRD negative

All subjects in cohorts 2 and 3 with bone marrow involvement at baseline had no detectable multiple myeloma cells in their bone marrow on day 14 or beyond.

All subjects had a prior autologous stem cell transplant, as well as prior exposure to a proteasome inhibitor and an immunomodulatory agent; 64% of subjects had previously received daratumumab or CD38 antibody. No dose-limiting toxicities and no Grade 3 or higher neurotoxicities or Grade 3 or higher cytokine release syndrome were observed. No subject had received tocilizumab or steroids.

It should be noted that these data presented above are current as of data cut-off date, are preliminary in nature and our CRB-401 study is not complete. There is limited data concerning long-term safety and efficacy following treatment with our bb2121 drug product. These data may not continue for these subjects or be repeated or observed in this ongoing study or future studies involving our bb2121 product candidate. It is possible that subjects for who initially respond to treatment with our bb2121 drug product may experience disease progression.

Our TCR product candidates and other preclinical research opportunities in cancer

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.

In collaboration with Kite Pharma, Inc., we are co-developing and, if approved, co-commercializing, second generation TCR product candidates directed against an antigen relating to certain cancers associated with the human papilloma virus, or HPV. HPV is the most common viral infection of the reproductive tract, and two viral strains, HPV type 16 and HPV type 18, are believed to cause a majority of cervical cancers and precancerous cervical lesions, and is associated with other urogenital cancers. Additionally, HPV infection has become established as an etiologic risk factor for oropharyngeal head and neck cancers. 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.

We are collaborating with Medigene AG, through its subsidiary Medigene Immunotherapies GmbH, to jointly discover and develop TCR product candidates directed against up to four antigens in the field of cancer. We are also independently researching and developing other CAR T cell 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.

19

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 manufacturing cycle. 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 following mobilization via a colony stimulating factor (or alternatively, by bone marrow harvest). 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. We will be using our updated drug product manufacturing process with the objective of increasing the vector copy number and the percentage of transduced cells in the LentiGlobin drug product in our ongoing Northstar-2 Study, our HGB-206 study under the amended protocol, and our planned Northstar-3 Study.

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.

20

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. In February 2016, we exclusively licensed to Celgene the right to develop and commercialize our bb2121 product candidate, pursuant to Celgene's exercise of its exclusive option under the collaboration arrangement. We have the obligation to continue conducting our ongoing CRB-401 study, but Celgene has the responsibility for the costs of further development and of commercialization. We retain an option to co-develop and co-promote the bb2121 product candidate in the United States. We will also work collaboratively with Celgene on potential additional anti-BCMA product candidates under this collaboration, including our anticipated next-generation anti-BCMA CAR T product candidate bb21217, which has been engineered for improved persistence as compared to bb2121.

Under the terms of 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 for up to two product candidates selected for development under the collaboration, the first of which is our bb2121 product candidate. 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 exclusively licensed to Celgene the worldwide rights to develop and commercialize the bb2121 product candidate. We may elect to co-develop and co-promote the bb2121 product candidate 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 bb2121 product candidate, then we will not be permitted to exercise our option to co-develop and co-promote any future product candidates under the collaboration.

Celgene is solely responsible for all costs and expenses of manufacturing and supplying the bb2121 product candidate and for any other product candidates arising from the collaboration that it exclusively licenses. 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.

In connection with its exercise of the option to exclusively in-license the bb2121 product candidate, Celgene paid 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, for each product candidate that is in-licensed by Celgene, including bb2121, 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 if we do not exercise our option to co-develop and co-promote in the United States. 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.

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.

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 for the treatment of certain cancers associated with HPV. 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 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, 2017, our patent portfolio includes the following:

- approximately 222 patents or patent applications that we own or have exclusively in-licensed from third parties related to lentiviral vectors and vector systems;
- approximately 62 patents or patent applications that we have non-exclusively in-licensed from third parties related to lentiviral vectors and vector systems;
- approximately 38 patents or patent applications that we own or have exclusively in-licensed from third parties, including eight that are co-owned with MIT, related to vector manufacturing or production;
- approximately seven patents or patent applications that have been non-exclusively in-licensed from third parties related to vector manufacturing or production;
- approximately 58 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from third parties related to therapeutic cellular product candidates;
- approximately 252 patents or patent applications that we own or have exclusively in-licensed or optioned from third parties related to oncology product candidates, including CAR T cell vector systems and manufacturing, T cell manufacturing, and therapeutic T cells;
- approximately 147 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from third parties related to gene editing compositions and methods; and
- approximately 22 patent applications that we have non-exclusively in-licensed from 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." From time to time, we also evaluate opportunities to sublicense our portfolio of patents and patent applications that we own or exclusively license, and we may enter into such licenses from time to time.

-thalassemia/SCD

The -thalassemia/SCD program 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 -thalassemia and SCD. As of January 31, 2017, we had an exclusive license to nine issued U.S. patents and one pending U.S. patent application. Corresponding foreign patents and patent applications include 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 any other 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 -thalassemia and SCD. As of January 31, 2017, we had an exclusive license (from RDF) to eight issued U.S. patents 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 any other 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. MIT/bluebird bio. The co-owned patent portfolio contains patents and patent applications directed to certain specific compositions of matter for lentiviral -globin expression vectors. As of January 31, 2017, we co-owned two issued U.S. patents and one pending U.S. patent 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 any 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.

Our -thalassemia/SCD research program also includes the additional patent portfolio described below.

- -thalassemia/SCD Product Candidate Licenses. We have in-licensed patents and patent applications that are directed to certain specific compositions of matter and methods for treating -thalassemia/SCD. As of January 31, 2017, we had an exclusive license to one pending U.S. patent application and 21 pending corresponding foreign applications. We expect any composition of matter or method patents, if issued from the pending patent 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 any other patents 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). In addition, as of January 31, 2017, we had a non-exclusive license to two issued U.S. patents, one pending U.S. patent application, and 26 pending corresponding foreign patent applications and two issued foreign patents (Europe and Mexico). We expect the issued composition of matter and method patents to expire in 2029 in the United States and in the rest of the world (excluding possible patent term extensions). We expect any composition of matter or method patents, if issued from the pending patent applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2029 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2029 (worldwide, excluding possible patent term extensions.

Cerebral Adrenoleukodystrophy (CALD)

The CALD program 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, 2017, we owned two U.S. patents and one pending U.S. patent application and 10 pending corresponding foreign applications and four issued foreign 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 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 in 2032 (worldwide, excluding possible patent term extensions). We expect any other patents 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).

Multiple Myeloma

The multiple myeloma program includes five patent portfolios, described below.

- Pasteur Institute. The in-licensed Pasteur patent portfolio contains patents and patent applications described above that are directed towards aspects of our lentiviral vectors utilized to produce our bb2121 product candidate for multiple myeloma.
- 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 bb2121 product candidate for multiple myeloma. In addition, the RDF portfolio contains additional patent applications directed to aspects of our oncology program. As of January 31, 2017, we had an exclusive license (from RDF) to three issued patents and two pending U.S. patent 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 any 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).
- Biogen. The in-licensed patent portfolio from Biogen Inc., formerly Biogen Idec MA Inc. and referred to herein as Biogen, contains patents and patent applications directed towards aspects of T cell-based products that target BCMA. As of January 31, 2017, we had a co-exclusive license to eight issued U.S. patents and three pending U.S. patent applications and 10 pending corresponding foreign applications and 101 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 any 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).
- NIH. The in-licensed patent portfolio from NIH contains patent applications directed towards aspects of T cell-based products that target BCMA. As of January 31, 2017, we had an exclusive license to one pending U.S. patent 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 any 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. The bluebird bio patent portfolio contains patent applications directed to certain specific compositions of matter for generating CAR T cells. As of January 31, 2017, we owned four pending U.S. patent applications and 62 corresponding pending foreign patent applications and two 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 from 2035-2038 (worldwide, excluding possible patent term extensions). We expect any 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 2035-2038 (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 -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, -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, 2017, we owned, or have in-licensed from third parties other than the Pasteur Institute and RDF, two related pending provisional applications, two pending U.S. patent applications and 22 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 2032-2037 (excluding possible patent term extensions). We expect any 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 2032-2037 (worldwide, excluding possible patent term extensions).

Oncology platform (e.g., vectors, manufacturing, and T cell-based products)

Our T cell-based oncology platform and oncology research program, which is applicable to our multiple myeloma program and other potential programs in cancer, includes four 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 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, 2017, we had an exclusive license (from RDF) to three issued patents and two pending U.S. patent 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 any 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 and improved CAR T cell compositions. As of January 31, 2017, we owned four pending U.S. patent applications and five corresponding pending foreign patent applications; five families of pending U.S. provisional applications; and one pending PCT application. 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 2033-2036 (worldwide, excluding possible patent term extensions). We expect any 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 2033-2036 (worldwide, excluding possible patent term extensions).
- T Cell Manufacturing Methods License. We have in-licensed patents and patent applications that are directed to certain specific methods for generating CAR T cells. As of January 31, 2017, we had a nonexclusive license to one issued U.S. patent, one pending U.S. patent application, and 30 corresponding issued foreign patents. We expect the issued method patents to expire in 2026 (excluding possible patent term extensions). Further, we expect 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 2026 (excluding possible patent term extensions). We expect any 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 2026 (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 and related methods of treatment. As of January 31, 2017, we had a co-exclusive or exclusive license to one pending PCT application 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 any 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, 2017, we have an exclusive license to one issued U.S. patent and ten corresponding foreign patents and co-own a pending PCT application to another particular target antigen. We expect the issued composition of matter patent to expire in 2025 (excluding possible patent term extensions). 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 any 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, 2017, we have an exclusive license to two issued U.S. patents, one pending U.S. patent application and ten corresponding foreign patents; have an exclusive license to a pending PCT application; and co-own a pending PCT application, to another particular target antigen. We expect the issued method of use patents to expire in 2029 (excluding possible patent term extensions). 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 from 2029-2036 (worldwide, excluding possible patent term extensions). We expect any 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 2029-2036 (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 -thalassemia, SCD, oncology and other programs. As of January 31, 2017, we had an exclusive/co-exclusive license to five issued U.S. patents and one pending U.S. patent application and 60 corresponding foreign patents and seven 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 any 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, 2017, 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 any 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 -thalassemia, SCD, oncology and other programs. As of January 31, 2017, we had an exclusive license to one issued U.S. patent and seven pending U.S. patent 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 any 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, 2017, we also had a non-exclusive license to one pending U.S. patent 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 any 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, 2017, we had an exclusive license to 2 pending U.S. applications and one corresponding issued foreign patent and 18 pending foreign patent applications related to our gene editing platform. We expect the issued composition of matter patens to expire in 2033 (excluding possible patent term extensions). We expect other 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 any 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, 2017, we also had a non-exclusive license to one pending U.S. application and 19 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 any 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, 2017, we owned seven families of provisional applications 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 2037 (worldwide, excluding possible patent term extensions). We expect any 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 2037 (worldwide, excluding possible patent term extensions). As of January 31, 2017, we co-owned (with Cellectis) two pending U.S. applications and 12 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 last patent in the Inserm licensed patent portfolio expired in February of 2016. 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 107 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 18 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 from 2017-2023. 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 29 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, non-clinical 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.

Biogen

In August 2014, we entered into a license agreement with Biogen, pursuant to which we co-exclusively licensed certain patents and patent applications directed towards aspects of T cell-based products that target BCMA. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date between 2020 and 2032. Biogen retains the right to practice and use the licensed patents in the licensed field and territory. We have the right to grant sublicenses to third parties, subject to certain conditions. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our bb2121 product candidate, we will be obligated to pay Biogen a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement. Additionally, we have assumed certain development and regulatory milestone obligations and must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to $24.0 million in the aggregate for a licensed product upon the achievement of these milestones. We may unilaterally terminate the license agreement at any time with prior written notice to Biogen. Either party may terminate the license in the event of the other party’s material breach upon notice and an opportunity for the breaching party to cure. Either party may also terminate the agreement in the event bankruptcy proceedings are opened against the other party and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration of all patent rights covered by the agreement or ten 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 in a U.S. patent, currently expected to expire in 2032.

NIH

In August 2015, we entered into a license agreement with the NIH, pursuant to which we exclusively licensed certain patents and patent applications directed towards aspects of T cell-based products that target BCMA. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date in 2033. NIH retains the right to practice the intellectual property licensed under the agreement on behalf of the government of the United States. We have the right to grant sublicenses to third parties, subject to certain conditions. For each such sublicense we grant we must pay the NIH a fee. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our bb2121 product candidate, we will be obligated to pay the NIH a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement. Additionally, we have assumed certain development and regulatory milestone obligations and must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to $9.7 million in the aggregate for a licensed product upon the achievement of these milestones. We may unilaterally terminate the license agreement at any time with prior written notice to the NIH. The NIH may terminate the license in the event of our material breach upon notice and following an opportunity for us to cure the material breach. The NIH may also terminate the agreement in the event bankruptcy proceedings are opened against us and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration

of the patent rights covered by the agreement. 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 2033.

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, and our preclinical T cell-based cancer immunotherapy product candidates. These efforts include the following:

- -thalassemia: The current standard of care for the treatment of -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. A number of different approaches are under investigation that seek to improve the current standard of care treatment options, including iron modulating agents and fetal hemoglobin regulators. In addition, some patients with -thalassemia receive HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. In addition, there are a number of academic and industry-sponsored research and development programs to improve allogeneic HSCT, or the tolerability and safety of haploidentical HSCT, while increasing the availability of suitable donors. These programs include a modified donor T cell therapy to be used in conjunction with haploidentical HSCT that is in an ongoing Phase I/II study supported by Bellicum Pharmaceuticals, Inc.; and an adjunctive T cell immunotherapy treatment in conjunction with allogeneic HSCT that is in an ongoing Phase I/II study supported by Kiadis Pharma. Acceleron Pharma, Inc. is investigating Luspatercept (ACE-536), a subcutaneously-delivered protein therapeutic that targets molecules in the TGF- superfamily, which is currently in a Phase III clinical trial in subjects with -thalassemia. There are also several different groups developing other approaches for -thalassemia, some of which use a similar ex vivo autologous gene therapy 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 -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), which has announced plans to initiate a Phase I clinical study using zinc finger nuclease-mediated gene-editing techniques in hemoglobinopathies including -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. In addition, there are a number of academic and industry-sponsored research and development programs to improve allogeneic HSCT, or the tolerability and safety of haploidentical HSCT, while increasing the availability of suitable donors. These programs include a modified donor T cell therapy to be used in conjunction with haploidentical HSCT that is in an ongoing Phase I/II study supported by Bellicum Pharmaceuticals, Inc. A number of different therapeutic approaches are under investigation targeting the various aspects of SCD pathophysiology, including: antibodies to p-selectin including crizanlizumab which recently completed a Phase II study supported by Novartis AG;

pharmaceutical grade L-glutamine, for which Emmaus Life Sciences, Inc. (which is under contract for Generex Biotechnology Corporation to acquire a controlling interest) completed a Phase III study and submitted an NDA in 2016; hemoglobin modifiers to prevent the sickling of RBC, including GBT440 in a Phase III study supported by Global Blood Therapeutics, Inc.; 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); 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); and Sangamo BioSciences Inc. (through its partnership with Biogen) which has announced plans to investigate the use of zinc finger nuclease-mediated gene-editing techniques in hemoglobinopothies including SCD, although to our knowledge no clinical studies have been initiated. 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.

- 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.
- Relapsed/Refractory Multiple Myeloma: The current standard of care for relapsed/refractory multiple myeloma includes IMIDs (e.g., thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), monoclonal antibodies (e.g., daratumamab, elotumuzumab), cytotoxic agents, and in some cases, HSCT. There are several groups developing autologous T cell therapies for relapsed/refractory multiple myeloma that use a similar autologous ex vivo approach, but a different target antigen, BCMA single-chain variable fragment or, we believe, cell processing techniques. These programs include: an anti-BCMA CAR T cell therapy that is currently in a single-center Phase I study by the University of Pennsylvania (in collaboration with Novartis AG); an anti-NY-ESO TCR T cell therapy that is currently in a Phase I/II study being supported by Adaptimmune Inc. (in collaboration with GlaxoSmithKline plc); and preclinical anti-BCMA CAR T programs announced by Juno Therapeutics, Inc. and Kite Pharma, Inc. In addition to these autologous T cell-based approaches, Cellectis SA has disclosed a preclinical program for an allogeneic BCMA CAR T cell therapy. There are also antibody-based therapies being developed by several groups, including a bispecific antibody therapy currently in a Phase I study supported by Amgen Inc., an antibody drug conjugate therapy currently in a Phase I study supported by GlaxoSmithKline plc, and those being developed in preclinical programs announced by Celgene, Five Prime Therapeutics, Inc., Janssen Pharmaceutical Companies of Johnson & Johnson, and Pfizer Inc.
- T cell-based immunotherapies in oncology: A number of pharmaceutical companies and academic collaborators are researching and developing T cell-based immunotherapies in oncology, in addition to the multiple myeloma programs described above. These include: 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, some of which are planning to apply for marketing approval in the United States in 2017.

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