bluebird bio, Inc.
Form 10-K
February 25, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2014

OR

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

Commission File Number: 001-35966

bluebird bio, Inc.

(Exact Name of Registrant as Specified in Its Charter)

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

150 Second Street

Cambridge, Massachusetts 02141

(Address of Principal Executive Offices) (Zip Code)

(339) 499-9300

(Registrant's Telephone Number, Including Area Code)

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

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

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

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

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

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

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

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

The aggregate market value of common stock held by non-affiliates of the registrant based on the closing price of the registrant's common stock as reported on the Nasdaq Global Select Market on June 30, 2014, the last business day of the registrant's most recently completed second quarter, was $798,893,699.

As of February 18, 2015, there were 32,566,331 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 2015 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to

which this report relates.

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FORWARD-LOOKING STATEMENTS

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

- the initiation, timing, progress and results of our preclinical and clinical studies, and our research and development programs;
- our ability to advance product candidates into, and successfully complete, clinical studies;
- our ability to advance our viral vector manufacturing and transduction capabilities;
- the timing or likelihood of regulatory filings and approvals;
- the 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 or obtain additional grant funding;
- our financial performance;
- developments relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

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

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

PART I

Item 1. Business

Overview

We are a clinical-stage biotechnology company committed to developing potentially transformative gene therapies for severe genetic and rare diseases and in the field of T cell-based immunotherapy. With our lentiviral-based gene therapy and gene editing capabilities, we have built an integrated product platform with broad potential application in these areas.

Many diseases have a genetic aspect whereby a dysfunctional gene linked to a disease is passed down from generation to generation and causes the disease. For the treatment of severe genetic and rare diseases, gene therapy seeks to introduce a functional copy of the defective gene into a patient's own cells, a process called gene transfer. In this context, we believe that gene therapy has the potential to change the way these patients are treated by correcting the underlying genetic defect that is the cause of their disease, rather than offering solutions that only address their symptoms. Accordingly, we believe gene therapy has the potential to provide transformative disease modifying effects with life-long clinical benefits based on a single therapeutic administration.

In the gene transfer process, a functional gene is typically delivered and incorporated into a patient's cells using viral vectors, which are based on naturally-occurring viruses that have been modified to take advantage of the virus' natural ability to introduce genes into human cells. However, unlike naturally-occurring viruses, which replicate following infection of a target cell and can infect new cells, gene therapy viral vectors are genetically modified to be non-replicating. Gene transfer using a viral vector is called transduction and the resulting gene-modified cells are called transduced cells. Transduction can be accomplished through either ex vivo or in vivo delivery of the vectors. In the ex vivo approach, cells are transduced outside of the patient's body and the modified cells are transplanted back into the patient. In the in vivo approach, vectors are introduced directly into the patient's body to deliver the desired gene to the target cell.

A growing body of gene therapy-based clinical data, the establishment of regulatory guidelines to govern the development and approval of gene therapy products and increased investment from the biopharmaceutical industry has allowed gene therapy to emerge as a potentially important new therapeutic modality for patients with significant unmet medical need. We believe we are particularly well-positioned to drive the continued advancement of gene therapy technology for the treatment of severe genetic and rare diseases and for T cell-based immunotherapy, initially in oncology. We have assembled extensive expertise in viral vector design, manufacturing and gene transfer, translational research and development capabilities, a broad intellectual property estate, an experienced management team and a world-class group of scientific advisors.

We and our scientific collaborators have generated what we believe is human proof-of-concept data for our gene therapy platform in three underserved diseases, each of which has been granted orphan drug status by U.S. and European regulatory authorities. We are conducting a Phase II/III clinical study, called the Starbeam Study, with our most advanced product candidate, Lenti-D,™ to evaluate its safety and efficacy in subjects with childhood cerebral adrenoleukodystrophy, or CCALD, a rare, hereditary neurological disorder affecting young boys that is often fatal. We also are conducting three clinical studies of our next most advanced product candidate, LentiGlobin® in a variety of rare, hereditary blood disorders that often lead to severe anemia and shortened lifespans: a global Phase I/II study, called the Northstar Study, for the treatment of -thalassemia major; a single-center Phase I/II study in France (HGB-205) for the treatment of -thalassemia major and severe sickle cell disease, or SCD; and a Phase I study in the United States (HGB-206) for the treatment of severe SCD.

In March 2013, we announced a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel, disease-altering gene therapies in oncology. The collaboration focuses on applying gene therapy technology to genetically modify a patient's own T cells to target and destroy cancer cells. Such modified T cells, called chimeric antigen receptor, or CAR T cells, have been shown by academic and corporate researchers to have beneficial effects in human clinical trials for patients with a variety of lymphomas. The multi-year research and development collaboration has the potential to lead to the development and commercialization of multiple CAR T cell products, and we expect the first product candidate from this collaboration to enter clinical trials in early 2016.

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

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

Utilizing our gene therapy platform, we are developing product candidates comprising the patient's own gene-modified HSCs. Clinical proof-of-concept already exists for allogeneic hematopoietic stem cell transplant, or HSCT, an approach of treating a patient with HSCs contributed by a donor other than the patient that contain the properly functioning copy of the gene whose mutation has caused the underlying disease. However, this approach has significant limitations, including difficulties in finding appropriate genetically-matched donors and the risk of transplant-related rejection, graft-versus-host disease 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 CCALD, ß-thalassemia major and severe SCD and for T cells is in oncology, we believe our gene therapy platform has broad therapeutic potential in a variety of indications. We believe that our vectors can be used to introduce virtually any gene into a cell and have the potential to be manufactured on a commercial scale reproducibly and reliably, as each new vector is produced using substantially the same process. We also take advantage of lentivirus' ability to transduce HSCs more efficiently than other vectors, such as those derived from another virus used in gene therapy approaches, called adeno-associated virus, or AAV, which gives us the potential to address diseases in a variety of cell lineages beyond those that are derived from HSCs, such as microglia (useful for CCALD), red blood cells (useful for ß-thalassemia and SCD), T cells (useful for cancer and immunology) and others.

The potential of gene therapy to address severe genetic and rare diseases

Gene therapy has been an evolving field for the last 20 years that has been characterized by great hope and potential. Gene therapy is an approach to treating disease through the introduction of a desired gene or gene sequence into a patient's own cells to modulate or enhance the activity of such cells. Each person's hereditary genetic material is encoded by deoxyribonucleic acid, or DNA, in sequences of genetic code called genes. Gene expression patterns influence cell functionality by controlling protein production, either directly or through other indirect regulatory mechanisms. A mutation, or alteration, in the gene or in sequences that control the expression of that gene can cause proteins to be produced aberrantly in the cell, which can cause disease.

Gene therapy represents a unique opportunity to change the way patients with severe genetic and rare diseases are treated by addressing the underlying cause of their disease, rather than offering solutions that focus only on their symptoms. By correcting the underlying genetic defect, we believe gene therapy can provide transformative disease modifying effects—potentially with life-long clinical benefits based on a single therapeutic administration.

Our belief in the potential of gene therapy to become a viable therapeutic modality is supported by several recent developments, including the following:

- Growing body of promising clinical results. Over the last several years, a number of clinical studies of gene therapies have shown promising efficacy and safety results in conditions such as multiple retinal diseases, adrenoleukodystrophy, or ALD, ß-thalassemia major, heart failure, lipoprotein lipase deficiency, various primary immunodeficiencies, hemophilia and Parkinson's disease. In addition, a number of clinical studies of CAR T therapies have shown promising efficacy and safety results in a variety of B cell malignancies.
- Significant design, manufacturing and process improvements. In recent years, we and others have designed new viral vectors with improved safety profiles over earlier generation vectors. Improvements in viral vector manufacturing techniques have also enabled the production of more potent and efficient viral vectors on a commercially viable scale.

- Growing support from regulators for gene therapy. In 2012, the European Medicines Agency, or EMA, approved a gene therapy product called Glybera, which is the first gene therapy product approved by regulatory authorities anywhere in the Western world. Although the U.S. Food and Drug Administration, or the FDA, has not yet approved any human gene therapy product, it has provided guidance for the development of gene therapy products. For example, the FDA has established the Office of Cellular, Tissue and Gene Therapies, or OCTGT, within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of cell and gene therapy products, and the Cellular, Tissue and Gene Therapies Advisory Committee, or CTGTAC, to advise CBER on its reviews. In addition, the FDA and EMA have issued a growing body of clinical, preclinical, chemical, manufacturing and control, or CMC and other guidelines, all of which are intended to facilitate industry's development of gene therapy products.
- Growing investment from the pharmaceutical and biotechnology industries. Companies such as GlaxoSmithKline plc, Sanofi/Genzyme Corporation, BioMarin Pharmaceutical Inc., Baxter International Inc., Shire plc, Biogen Idec, Novartis AG, Juno Therapeutics, Inc. and Kite Pharma, Inc. are currently advancing programs in gene therapy or in CAR T therapies for oncology.

Our gene therapy platform and proprietary lentiviral vectors

Our gene therapy platform and product candidates 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 existing DNA. 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 the HIV-1 virus 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 chromosome. 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 during cell division along with the rest of the cell's chromosomal DNA. Therefore, subsequent dividing cells resulting from the originally transduced cell will also carry the newly inserted gene sequence. The power of lentiviral vectors is sustained expression: a single insertion of a functional gene into a dividing cell can have a multiplying effect on multiple downstream cells. 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 thus 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. This integration pattern difference has been published in several studies, showing that lentiviral vectors have demonstrated an improved safety profile over gamma-retrovirus 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.

Our focus on Hematopoietic Stem Cells (HSCs)

Our gene therapy platform takes advantage of lentiviral vectors' ability to stably integrate into the target cell's chromosome by focusing on diseases we can treat through genetic modification of hematopoietic stem cells, or HSCs, which when reintroduced back into the patient, differentiate into numerous other cell lineages, as depicted below. We believe our initial clinical indications—CCALD, ß-thalassemia major 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 microglia (useful for CCALD), red blood cells (useful for ß-thalassemia and SCD), 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

The delivery of a gene therapy product requires several steps, as illustrated in the figure below. 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 or antibody fragment the viral vector will carry. The use of multiple plasmids is an important safety step designed to further prevent the resulting lentiviral vectors from being able to replicate and cause infection on their own.
2. For the treatment of severe genetic and rare diseases, a sample of the patient's own HSCs is extracted and isolated through a standard process known as apheresis, where HSCs are first mobilized into the blood stream from the bone marrow using a

routinely-used pharmaceutical agent and then collected from the patient's blood. In some cases, such as for the treatment of SCD, HSCs are extracted directly from the patient's bone marrow. A patient's T cells are also extracted and isolated using a standard mobilization procedure.

3. The lentiviral vector is mixed with the patient's isolated HSCs or T cells ex vivo. In the case of HSCs, 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. In the case of T cells, this leads to the creating of modified T cells with chimeric antigen receptors. 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 HCST) to remove all 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. Following successful engraftment, we anticipate that clinical benefits for Lenti-D in CCALD, indicated by prevention of major functional disabilities, stabilization of NFS and Loes score and resolution of gadolinium enhancement, will begin to become evident within 24 months of transplant, and that clinical benefits for LentiGlobin in ß-thalassemia and SCD, indicated by reduction or elimination of blood transfusion requirements, number of in-patient hospitalization days (post-transplant discharge) and, for SCD, several additional endpoints, will begin to become evident within 6-12 months of transplant.

We believe that our approach has several potential advantages over current treatment options for CCALD, ß-thalassemia and SCD, including the following:

- Single administration with potential life-long benefit. Our process allows us to potentially arrest, correct or treat a disease with a single therapeutic administration as many of the corrected cells will live in the patient's body and have the potential to deliver long-term, and possibly life-long, effects.
- We know exactly what gene to insert. We are initially pursuing diseases where the genetic abnormality is known and is found in a single gene, known as monogenic diseases. We therefore know what we are correcting and exactly what gene sequence to insert into the patient's cells, thus mitigating against the uncertainty of the disease biology.
- Allogeneic HSCT provides proof-of-concept for our approach. We are currently pursuing clinical indications for which allogeneic HSCT is already a proven therapeutic option. Clinical proof-of-concept already exists for the diseases we are targeting via allogeneic 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.
- We use the patient's own cells. By using the patient's own isolated HSCs, we believe our approach will eliminate many of the challenges associated with allogeneic HSCT, such as the limited availability of optimally matched donors and risks of transplant rejection that often result in serious adverse events, such as graft-versus-host disease. Even where allogeneic HSCT is deemed successful, many patients are required to comply with prolonged immunosuppressive drug regimens that increase the risk of opportunistic infections and other adverse events.
- We modify our target cells ex vivo. By inserting the new functional DNA into the cells ex vivo, we reduce the risk of adverse events and remove one of the key biological complexities of any therapeutic—getting a drug directly to the target cells.
- Administration of our drug product is consistent with existing stem cell transplant practices. The final step of our process, in which patients are myeloablated and then transfused with the finished drug product, is consistent with widely adopted stem cell transplant clinical practices and infrastructure already in use.
- Value proposition to patients, families, health care providers and payors. Given the potentially dramatic clinical and life-long benefits anticipated from such therapies delivered through potentially a single administration, we believe the value proposition for patients, families, health care providers and payors would be significant.

Our product candidate pipeline

The following table summarizes key information on our development programs.

Our most advanced product candidate is called Lenti-D, which we are developing to treat patients with CCALD, the most severe form of ALD. We are conducting a Phase II/III clinical study of Lenti-D in the United States, which we refer to as the Starbeam Study, to examine the safety and efficacy of Lenti-D in preserving neurological function and stabilizing cerebral demyelination in subjects with CCALD. In January 2015, we received regulatory authority approval for the Starbeam Study from the Medicines and Healthcare Products Regulatory Agency (MHRA) in England. We also expect to activate a site for the Starbeam Study in France, pending approvals from the applicable regulatory authorities. Our next most advanced product candidate is called LentiGlobin, which we are developing to treat patients with ß-thalassemia and severe SCD. We are conducting a Phase I/II clinical study of LentiGlobin, which we refer to as the HGB-205 Study, in subjects with ß-thalassemia major and severe SCD. We also have initiated a second Phase I/II clinical study in the United States, Australia and Thailand for LentiGlobin, which we refer to as the Northstar Study, for the treatment of ß-thalassemia major. We have also initiated a Phase I study of LentiGlobin in the United States (HGB-206) for the treatment of severe SCD.

In March 2013, we announced a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel disease-altering gene therapies in oncology. The collaboration focuses on applying gene therapy technology to genetically modify a patient's own T cells to target and destroy cancer cells. Such modified T cells, called chimeric antigen receptor, or CAR, T cells have been shown by academic and corporate researchers to have beneficial effects in human clinical trials for patients with a variety of lymphomas. The multi-year research and development collaboration has the potential to lead to the development and commercialization of multiple CAR T cell products and we expect the first product candidate from this collaboration to enter clinical trials in early 2016. See "—Our strategic alliance with Celgene."

Our Lenti-D opportunity

Adrenoleukodystrophy

Adrenoleukodystrophy is a rare X-linked, inherited, neurological disorder that is often fatal. ALD is caused by mutations in the ABCD1 gene which encodes for a protein called the ALD protein, or ALDP, which plays a critical role in the breakdown and metabolism of very long-chain fatty acids, or VLCFA. Without functional ALDP, VLCFA accumulate in cells in the body, including microglial cells which are found in the brain and spinal cord. The build-up of VLCFAs causes damage to the myelin sheath, a protective and insulating membrane that surrounds nerve cells in the brain. This damage can result in decreased motor coordination and function, visual and hearing disturbances, the loss of cognitive function, dementia, seizures, adrenal dysfunction and other complications, including death. The worldwide incidence rate for ALD is approximately one in 20,000 newborn males.

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

- CCALD (Childhood cerebral adrenoleukodystrophy): The most severe form of ALD is CCALD. CCALD accounts for about 30-40% of patients diagnosed with ALD and presents in young boys. CCALD is characterized by progressive destruction of myelin, leading to severe loss of neurological function and eventual death. In boys affected by CCALD, learning and behavioral problems are often observed in mid-childhood between the ages of 3 and 15 years (median age 7). In the absence of intervention, boys affected by CCALD typically experience rapid degeneration into vegetative state, and ultimately death within a decade of diagnosis.
- AMN (Adrenomyeloneuropathy): AMN which typically develops in adults aged 21 years and older, is the most common neurological form of ALD, accounting for 40-45% of all patients diagnosed with ALD. All patients with AMN present with more slowly progressive symptoms resulting from (non-inflammatory) disruption of the axons (which are a fundamental component of the central nervous system that allows nerve signals to be transmitted) in the spinal cord. Approximately 40% of these patients have or will develop cerebral disease similar to CCALD, with varying degrees of associated inflammation.
- ACALD (Adult Cerebral ALD): ACALD typically develops in males aged 21 years and older. It is also very severe, with progression of neurologic symptoms that parallels the course of CCALD. Recent published research shows that ACALD accounts for approximately 25% of all patients diagnosed with ALD.

Limitations of current treatment options

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

Allogeneic HSCT is preferably performed early in the course of the disease, ideally using an unaffected matched sibling HSC donor to minimize complications. However, the majority of allogeneic HSCT procedures for CCALD are carried out with non-sibling matched donor cells, partially matched related or unrelated donor cells including umbilical cord blood cells because a matched sibling donor is not available in most cases. The difficulty of finding a suitable sibling-matched donor is one of the primary drawbacks of this approach. Allogeneic HSCT is associated with

significant morbidity and mortality, particularly in patients who undergo non-sibling-matched allogeneic HSCT. Complications of allogeneic HSCT include a 10-30% risk of engraftment failure in unrelated Human-Leukocyte-Antigen, or HLA, matched patients, a 12-16% incidence of life-threatening infection, and an approximately 30% risk of graft-versus-host-disease, or 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 in CCALD patients can lead to significant mortality rates, particularly for patients treated with cells from a donor who is not a matched sibling. In addition, because of the need for long-term immunosuppression following allogeneic HSCT, there is a prolonged risk of opportunistic infections and other serious side effects associated with immunosuppressive drugs.

Moreover, of the approximately 80 boys who are born with CCALD each year in the United States and European Union, we estimate that between 20% and 50% may have disease so advanced at the time of diagnosis that a beneficial outcome from treatment would be unlikely. This is attributed to rapid disease progression and difficulty with early diagnosis, as the initial presentation of the signs and symptoms of CCALD are frequently misdiagnosed. Newborn screening through a simple and inexpensive blood test is being

developed to enable earlier detection of CCALD and is available in several states. Based in part on the fact that several states have approved or are currently considering universal newborn screening for ALD, it is our expectation that newborn screening will be widely adopted in the United States within the next five years, and potentially elsewhere, providing for the opportunity to identify more boys for proactive monitoring of disease symptoms and early disease intervention.

Our Lenti-D product candidate

We are developing our Lenti-D product candidate as a potential one-time treatment to halt the progression of CCALD. 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 CCALD. Upon successful engraftment of our Lenti-D product candidate, we expect that microglia in the brain derived from the transduced HSCs will correct the metabolic abnormalities resulting from excess VLCFA and stabilize the demyelination and cerebral inflammation characteristic of CCALD.

We treated the first subject in the Starbeam Study in the United States in 2013. In January 2015, we received regulatory authority approval for the Starbeam Study from the Medicines and Healthcare Products Regulatory Agency (MHRA) in England. We also expect to activate a site for the Starbeam Study in France, pending approvals from the applicable regulatory authorities. 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. See "Item 1A. Risk Factors—The results from our Starbeam Study may not be sufficiently robust to support the submission of marketing approval for our Lenti-D product candidate. Before we submit Lenti-D for marketing approval, the FDA and the EMA may require us to enroll additional subjects, conduct additional clinical studies, or evaluate subjects for an additional follow-up period." Lenti-D has been granted Orphan Drug status by the FDA and EMA for CCALD.

Clinical development of our Lenti-D product candidate

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

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

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

CCALD patient populations.

Three primary clinical measurements of CCALD disease progression

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

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

Symptoms	Score
Loss of communication*	3
No voluntary movement*	3
Cortical blindness*	2
Tube feeding*	2
Wheelchair required*	2
Total incontinence*	2
Swallowing/other CNS dysfunctions	2
Spastic gait (needs assistance)	2
Hearing/auditory processing problems	1
Aphasia/apraxia	1
Visual impairment/fields cut	1
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Episodes of incontinency	1
Nonfebrile seizures	1
Total	25

*Major Functional Disabilities (MFDs)

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

- The Loes score. The Loes score is a 34-point scale specifically designed to objectively measure the extent of central nervous system disease burden based on brain magnetic resonance imaging, or MRI, studies. The Loes score measures the extent and location of brain abnormalities such as the presence of white matter changes, degree of demyelination and the presence of focal or global atrophy. A Loes score of one or more (i.e., the presence of any such abnormalities) indicates significant disease, and patients with a Loes score of 10 or more generally are not considered to be good candidates for allogeneic HSCT due to the advanced stage of the disease.
- Gadolinium enhancement. One of the hallmarks of inflammatory disease in ALD patients is the presence of a compromised blood-brain barrier behind the leading edge of demyelinating lesions in the brain. This can be assessed using a contrast agent called gadolinium in brain MRI studies. Evidence of gadolinium enhancement in the brain in a MRI study, referred to by clinicians as a gadolinium positive result, suggests that neuroinflammation is present and the blood-brain barrier has been compromised, which in published studies has been shown to be a predictive biomarker of ALD disease progression.

Summary of findings

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

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Untreated, CCALD patients progress to dismal outcomes. In the untreated cohort, the median overall survival was 92 months (7.7 years) and the estimated probability of survival at five years was 55%. Although informative, survival data must be considered in light of the fact that supportive measures may be used to sustain life after progression to a vegetative state.

- Baseline disease severity, as assessed by NFS and Loes scores, were good predictors of survival. In both the untreated and treated cohorts, significantly lower mortality rates were seen in patients with lower baseline NFS and Loes scores than in those with higher scores.

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

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

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

- MFDs occurred in the majority of the untreated cohort who showed evidence of gadolinium enhancement in brain MRI. The majority of untreated subjects (67%) had progressive disease resulting in premature MFD or death during the study period, with 91% (19/21) of gadolinium positive subjects dying or having an MFD during the study period.
- Allogeneic HSCT was associated with disease stabilization. Despite the significant risk of morbidity and mortality associated with allogeneic HSCT, successful transplantation was shown to provide clinically meaningful benefit to patients with CCALD, particularly those with early-stage disease. Of the subjects who were evaluable at 24 months post-allogeneic-HSCT, 49% (N=51) of the allogeneic-HSCT cohort remained MFD-free. Allogeneic HSCT was also associated with resolution of gadolinium enhancement. Of those patients who would meet eligibility criteria for the Starbeam study (baseline NFS of zero or one, gadolinium-positive prior to allogeneic HSCT, baseline Loes between 0.5 and nine, inclusive and did not have a matched sibling), four of 21 (19%) patients developed an MFD within 24 months post-allogeneic HSCT.
- Consistent with published literature, allogeneic HSCT, particularly with unmatched/unrelated donors, was associated with clinically significant morbidity and mortality.
- Morbidity: Post-allogeneic HSCT, engraftment failure occurred in 12 of 65 (19%) patients, 10 of whom (83%) were transplanted with unrelated donor cells. Despite prophylaxis, the GVHD rate was reported in 34 of 58 evaluable subjects (59%), including acute GVHD in 26 (45%) patients and chronic GVHD in 12 (19%) patients. Due to the requirement for myeloablation prior to HSCT, the occurrence of GVHD and the requirement for immunosuppressive therapy post-allogeneic HSCT, allogeneic HSCT is associated with a substantial risk of life-threatening infection. Infections were the most commonly reported serious adverse event, with at least one serious infection reported in 19 (29%) patients post-allogeneic HSCT. The substantial morbidity associated with allogeneic HSCT for CCALD supports evaluating Lenti-D in the Starbeam Study as an alternative therapeutic option that is expected to avoid the issues of immune incompatibility seen with allogeneic HSCT.
- Mortality: Post-allogeneic HSCT, the 100-day mortality rate was 8% and the overall one-year mortality rate was 19%. The estimated probability of two and five year survival rates post-allogeneic HSCT were 82% and 74%, respectively. As anticipated from the published literature, analysis of survival by type of donor (matched sibling versus other) showed that the proportion of deaths through the observation period post- allogeneic HSCT was lower in matched-sibling donor cases than in other allogeneic HSCT cases. The majority of allogeneic HSCT patients (46 patients; 71%) were transplanted with unrelated donor cells given the limited availability of HLA-matched sibling donors. As a result of this analysis, we determined to exclude patients with a sibling-matched donor from the Starbeam Study.

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

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

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

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

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

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

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

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

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

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

Phase II/III Starbeam clinical study

In October 2013, we treated the first subject in a Phase II/III clinical study, called the Starbeam Study, of our Lenti-D product candidate, to evaluate its safety and efficacy in subjects with CCALD. The study is designed as a single-dose, open-label, non-randomized, international, multi-center 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 CCALD. Subjects will be followed for 24 months post-transplant under this protocol. In accordance with applicable guidance from the FDA and EMA, we will be monitoring study subjects in a 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.

- Up to 15 subjects will be enrolled in the study to obtain at least 12 evaluable subjects that have been transplanted with the Lenti-D drug product. In the study, subjects must be age seventeen years or younger with a confirmed diagnosis of active CCALD, 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 10/10 HLA matched sibling HSCT donor will be excluded from the study.

Based on results from our retrospective ALD-101 Study and consultation with leading clinicians in the field of ALD, we have defined the primary efficacy endpoint in the Starbeam Study as the proportion of subjects who have no MFDs, as measured by NFS, at 24 months (±two months) post-transplant. Secondary efficacy evaluations, in each case measured at 24 months (±two months) post-transplant, capture the key assessments of CCALD 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 through 100 and 180 days post-transplant; 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 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 Lenti-D prior to a BLA submission. We are also conducting an observational study of subjects with CCALD treated by allogeneic HSCT referred to as the ALD-103 study. This study will collect efficacy and safety outcomes data in patients who are undergoing allogeneic-HSCT. We anticipate that Lenti-D safety and efficacy will be evaluated by the FDA and EMA in light of the data collected in the Starbeam Study as well as our retrospective ALD-101 study and our observational ALD-103 study.

Our LentiGlobin opportunity

ß-thalassemia

Overview

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

The clinical course of ß-thalassemia correlates with the degree of globin chain imbalance. Nearly 200 different mutations have been described in patients with ß-thalassemia. The clinical presentation varies widely, dependent largely upon the number and type of inherited mutation. Mutations can be categorized as those which result in little or no functional ß-globin production (ß°) and those which result in decreased functional ß-globin production (ß⁺). ß-thalassemia major refers to any mutation pairing that results in the need for chronic transfusions due to severe anemia, and is the clinical finding in patients with ß°ß° genotype as well as many with the ß°ß⁺ genotype. Affected patients produce as little as one to seven g/dL of hemoglobin (while a normal adult produces 12-18 g/dL of hemoglobin). Hemoglobin E, which is another ß-globin mutation and is usually asymptomatic, can also result in ß-thalassemia major when paired with the ß° or ß⁺ mutations.

ß-thalassemia is concentrated in populations of Mediterranean, South and Southeast Asian and Middle Eastern descent. It has been estimated that about 1.5% (80 to 90 million people) of the global population are carriers of ß-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. According to Thalassemia International Federation, about 288,000 patients with ß-thalassemia major are alive and registered as receiving regular treatment around the world, of which it is estimated that about 15,000 live in the United States and Europe. Due to the rarity of this disease in the United States, published research on the prevalence of ß-thalassemia in the United States is limited, although it is estimated that due to changing immigration patterns, 1.8 in 100,000 births in California are affected by ß-thalassemia.

Limitations of current treatment options

In geographies where treatment is available, patients with ß-thalassemia major receive chronic blood transfusion regimens aimed at maintaining steady state hemoglobin levels. These regimens consist of infusions with units of pRBC every three to five weeks, the timing of which is based predominantly on monitoring hemoglobin levels. Chronic blood transfusions can be effective at preventing the symptoms of childhood ß-thalassemia major, however, often lead to iron overload, which over time leads to mortality through iron-associated heart and liver toxicity. To prevent iron overload-associated risks, patients must adhere to therapeutic iron chelation regimens to reduce the iron overload. Poor compliance with chelation regimens remains a key challenge; it is estimated that with typical compliance, the overall life expectancy for a patient with transfusion-dependent ß-thalassemia is only 28 years. Even patients who are compliant with transfusion and iron chelation regimens can experience a reduced quality of life due to the burden of therapy and the fluctuating levels of hemoglobin on a month-to-month basis.

The only potentially curative therapy for ß-thalassemia today is allogeneic HSCT. However, because of the significant risk of transplant-related morbidity and mortality, transplants are offered primarily to pediatric patients with a matched sibling donor, which occurs in less than 25% of all cases. Allogeneic HSCT carries a significant risk of morbidity and mortality related to myeloablation), immunosuppressive medications, graft failure, GVHD and opportunistic infections. Overall, ß-thalassemia major remains a devastating disease with an unmet medical need.

In many developing countries where ß-thalassemia is more prevalent, such as Thailand, the lack of readily available chronic blood transfusions and optimal iron chelation regimens represents a significant societal challenge. In these countries, children with ß-thalassemia major have a poor prognosis and experience growth retardation, hepatosplenomegaly, or enlargement of the spleen, and skeletal deformities resulting from extra-medullary hematopoiesis. Ultimately, most die in childhood. We believe that safer therapies, such as those represented by our gene therapy approach, could offer a potential solution to the challenges of treating ß-thalassemia patients across the world.

Sickle cell disease

Overview

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

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

Limitations of current treatment options

Where adequate medical care is available, common treatments for patients with SCD include chronic blood transfusions and hydroxyurea. As is the case with ß-thalassemia, chronic transfusions pose a compliance burden and are associated with significant risks that often leads to mortality through iron-associated heart and liver toxicity. Patients must also adhere to daily iron chelation regimens. A significant number of patients with SCD find it difficult to adhere to hydroxyurea treatment regimens due in part to drug-related toxicities.

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

Our LentiGlobin product candidate

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

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

We have initiated a Phase I clinical study in the United States, called the HGB-206 Study, to evaluate the safety and efficacy of LentiGlobin in subjects with severe SCD.

LentiGlobin has been granted Orphan Drug status by the FDA and EMA for both -thalassemia and severe SCD, in January 2013 LentiGlobin was granted Fast-Track designation by the FDA for the treatment of beta-thalassemia major, and in January 2015, the FDA granted Breakthrough Therapy designation to LentiGlobin for the treatment of transfusion dependent patients with -thalassemia.

Clinical development of our LentiGlobin product candidate

Previous clinical experience with lentiviral gene therapy for ß-thalassemia major (the LG001 Study)

Between September 2006 and November 2011, three subjects with ß-thalassemia major were treated in France by our scientific collaborators in a Phase I/II study with autologous HSCs transduced ex vivo with an earlier generation of our LentiGlobin vector, called HPV569. We refer to the HSCs transduced ex vivo with the HPV569 vector as the HPV569 drug product. Clinical data and biological experience with one subject in this study (Subject Three) were first reported in Nature (2010), with follow-up data presented at the European Hematology Association Congress in June 2014.

Four subjects were enrolled in the LG001 Study, although only three subjects were actually treated with the HPV569 drug product—Subject One was ineligible due to pre-transplant complications. The other three subjects were successfully transplanted, however Subject Two received a dose of HPV569 drug product with cell counts well below current standards in transplant practice and failed to engraft. All subjects enrolled in the study required significant transfusion support prior to treatment. Below is a summary of the results for the two subjects with successful engraftment:

- Subject Three: During the first year post-transplant, Subject Three experienced a decline in both the volume and frequency of transfusion requirements and eventually became transfusion-independent approximately one year post-treatment. Adverse events considered to be treatment related were all attributable to study procedures or myeloablative conditioning, but not related to the HPV569 drug product.

- Subject Four: After transplant, Subject Four experienced delayed recovery of platelets and required platelet transfusion thrice weekly until day 100, with the last transfusion on day 122. Hemoglobin from gene therapy in reticulocytes was detectable early post-transplant, however the levels declined gradually. Subject Four is clinically stable and has fully engrafted two years post-treatment, but is producing only minimal amounts of new hemoglobin and, therefore, remains transfusion dependent. Adverse events considered to be treatment related were all attributable to study procedures or myeloablative conditioning, but not the HPV569 drug product.

All subjects from LG001 have been offered the possibility to enroll in the long term follow-up study, LTF-303, to evaluate long-term safety and efficacy post-transplant.

We believe the efficacy and safety results of the LG001 Study provided clinical proof-of-concept, as the lentiviral vector used in the study shares many features with our current LentiGlobin vector. In addition, the results of the LG001 Study were helpful in informing the design of our HGB-205 and Northstar clinical studies. Additionally, with improvements we have introduced into the vector manufacturing and transduction processes, we expect to obtain a higher proportion of gene-therapy modified HSCs in the drug product manufactured for the patients treated in the HGB-205 and Northstar clinical studies compared to what was achieved in the LG001 Study, which we believe will translate into improved clinical efficacy and in improved clinical benefit by virtue of increased production of normally functioning hemoglobin.

The HGB-205 Phase I/II clinical study for ß-thalassemia major and severe sickle cell disease

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

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

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

Preliminary Clinical Data from the HGB-205 Study

In December 2014, we presented preliminary clinical data from the HGB-205 study at the Annual Meeting of the American Society of Hematology, or ASH. As of December 1, 2014, two subjects with -thalassemia major had undergone infusion with LentiGlobin BB305 drug product in the HGB 205 study. Both of these subjects achieved rapid transfusion independence with near-normal hemoglobin levels and are producing steadily increasing amounts of ß-^{T87Q}-globin, similar to what may be expected from a successful allogeneic transplant, and as of December 1, 2014, had been free from the need for transfusions for 12 months and nine months, respectively. The third treated subject in the HGB-205 study, the first individual with sickle cell disease ever to be treated with gene therapy, has achieved engraftment, but at the time of the ASH annual meeting, it was too early post-transplant to draw any meaningful conclusions on clinical efficacy. Below is a table summarizing the preliminary clinical data from the HGB-205 study presented at the ASH annual meeting in December 2014:

	-Thalassemia Major		Severe Sickle Cell Disease
Patient	1201	1202	1204
Enrollment age/Sex	18/F	16/M	13/M

Country of birth	Syria	France	France
Genotype	0/ E	0/ E	S/ S
Transfusion requirements (mls/kg/year)	139	188	170
CD34+ VCN	1.5	2.1	1.2/1.0*
CD34+ cell count	8.9	13.6	5.6
($x10^6$/kg)			
Days to neutrophil engraftment	Day +13	Day +15	Day +37
HbA^{T87Q}/total Hb (g/dL)	7.7/11.0	9.6/13.4**	NA
Last study follow up (months)	12	9	1

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

**Hemoglobin levels represent data from the six-month follow up visit. Nine-month visit hemoglobin data not yet available.

In the HGB-205 study, treatment with LentiGlobin has been well tolerated, with no gene therapy-related Grade 3 or greater adverse events observed as of December 1, 2014.

The Northstar Phase I/II clinical study for ß-thalassemia major

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

Up to 15 adults will be enrolled in the study. Study subjects must be between 18 and 35 years of age with a diagnosis of ß-thalassemia major and receive at least 100 mL/kg/year of pRBCs or greater than or equal to eight transfusions of pRBCs per year in each of the two years preceding enrollment. The subjects must also be eligible for allogeneic HSCT. We are planning to amend the protocol for the Northstar Study to allow for the enrollment of adolescent subjects between 12 and 17 years of age.

Efficacy will be evaluated primarily by the production of ³2.0 g/dL of hemoglobin A containing ß$^{A\text{-}T87Q}$-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 the primary endpoint is that production of ³2.0 g/dL of hemoglobin A containing ß$^{A\text{-}T87Q}$-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 ß-thalassemia 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.

Preliminary Clinical Data from the Northstar Study

In December 2014, we presented preliminary clinical data from the Northstar Study at the ASH Annual Meeting. As of December 1, 2014, five subjects with -thalassemia major had undergone infusion with LentiGlobin BB305 drug product in the Northstar Study. The first two subjects treated in the Northstar Study had produced steadily increasing amounts of ^{T87Q}-globin and, as of December 1, 2014, had been free from the need for transfusions for five months and three months, respectively. As of December 1, 2014, three additional subjects had been infused, but at the time of the ASH annual meeting, it was too early to draw any meaningful conclusions on clinical efficacy for these subjects. Below is a table summarizing the preliminary clinical data from the Northstar Study presented at the ASH annual meeting in December 2014:

	1102	1104	1106	1107	1108
Patient					
Enrollment age/Sex	18/F	21/F	20/F	26/F	18/F
Country of birth	USA	Thailand	Pakistan	Australia	USA
Genotype	0/ E	0/ E	0/ 0	0/ 0	0/ +
Transfusion requirements (mls/kg/year)	137	153	197	223	144
CD34+ VCN	1.0/1.1*	0.7/0.7*	1.5	1.0	0.9
CD34+ cell count	6.5	5.4	13.5	15.0	7.9

($x10^6$/kg)					
Days to neutrophil engraftment	Day +17	Day +18	Day +29	Day +14	NA
HbA^{T87Q}/total Hb (g/dL)	3.8/8.6	0.27/9.8	6.8/9.6	0.34/9.6	NA
Last study follow up (months)	6	1**	3	1	<1

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

**Data includes two months of follow-up on safety only.

The HGB-206 clinical study for severe sickle cell disease

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

Up to 8 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 venoocclusive events, acute chest syndrome, history of an overt stroke, or echocardiographic evidence of an elevated tricuspid regurgitant jet velocity, an indicator of pulmonary hypertension. 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.

Our CAR T Cell Oncology Opportunity

In March 2013, we announced a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel, disease-altering gene therapies in oncology. The collaboration focuses on applying gene therapy technology to genetically modify a patient's own T cells to target and destroy cancer cells. Such modified T cells, called chimeric antigen receptor, or CAR T cells, have been shown by academic researchers to have beneficial effects in human clinical trials for patients with a variety of lymphomas. The multi-year research and development collaboration has the potential to lead to the development and commercialization of multiple CAR T cell products for a variety of liquid and solid tumor cancers. We expect the first product candidate from this collaboration to enter clinical trials in early 2016.

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 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 Rituxan in 1997, and since then, many other antibodies have received approval, including Herceptin, Avastin, Campath, Erbitux, and Vectibix. More recently, antibodies have been conjugated with cytotoxic drugs to increase activity. The first approved antibody drug conjugate was Mylotarg in 2000, followed by Adcetris in 2011 and Kadcycla 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, Yervoy became the first checkpoint inhibitor approved by the FDA. Recent clinical data from checkpoint inhibitors such as nivolumab and Keytruda have confirmed both the approach and the importance of T cells as promising tools for the treatment of cancer.

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

Our CAR T Technology

Like our programs for HSCs, our CAR T technology uses a customized lentiviral vector to alter T cells ex vivo, or outside the body, so that the T cells can recognize specific proteins on the surface of cancer cells or other diseased cells in order to kill those diseased cells. With our CAR T technology, 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 construct are transferred into the T cell DNA using a lentiviral vector. The number of cells is expanded until it reaches the desired dose. These genetically engineered cells, which will express the receptors that can recognize the specific proteins that are characteristic of specific cancers, are then infused back into the patient. Our entire T cell engineering process is rapid (complete in around ten days) and manufactures modified T cells in a sterile closed system.

When the engineered CAR 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

protein are destroyed, the engineered T cells decrease in number leaving a smaller number of T cells in the body as a form of immune surveillance against potential tumor regrowth. The genetically-engineered CAR 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 T cell technology also brings genomic engineering tools to the immunotherapy field. Using our gene editing homing endonuclease technology, we have a number of additional options to manipulate the genome of the cancer patient's T cells to further increase the specificity of the anti-tumor activity and to potentially make these cells even more potent. Specificity and potency are essential to the development of CAR T cell therapies that can effectively treat solid tumor cancers such as breast, prostate 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 CAR T cell therapy. This team is focused on the next generation of T cell engineering to discover and develop T cell product candidates to treat a variety of liquid and solid tumor cancers.

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 discovery research efforts. We are focused on utilizing homing endonuclease and megaTAL gene editing technologies in a variety of potential applications and disease areas, including for hematology and oncology. Homing endonucleases and MegaTALs are novel enzymes that provide a highly specific and efficient way to silence, edit, or insert genetic components into a 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 are the only monomeric naturally occurring proteins to bind DNA in a sequence specific fashion and cleave their target sites. MegaTALs are fusion proteins that combine homing endonucleases with the targeting domain of TALENs resulting in greater DNA sequence specificity and lower off target activity. We believe there are multiple advantages of homing endonucleases and MegaTALs compared to other gene editing technologies, most notably: they are naturally occurring gene-editing proteins, they are highly specific and efficient in cutting DNA and their compact size allows for delivery of multiple proteins. 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 HSCs isolated from the patient.

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

Although we intend to continue manufacturing our Lenti-D vectors in TTCFs, we are adapting our LentiGlobin vector production technology to a larger, suspension-based bioreactor process with the potential to scale from 100 to upwards of 1,000 liters in a single production run. So far, we have demonstrated successful production of LentiGlobin vectors on a small scale and have transferred 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 cells (our drug product)

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

1. Selection: We extract HSCs from peripheral blood mononuclear cells obtained from the patient's blood by apheresis (or alternatively, by bone marrow harvest) following mobilization via a colony stimulating factor. The process is carried out using existing hospital infrastructure and standard protocols currently in place for stem cell transplant procedures.
2. Pre-stimulation: The isolated HSCs are treated with a mixture of growth factors and additional proprietary processes 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 for a period of time to facilitate transduction and insertion of the therapeutic DNA into the chromosomes 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. Just prior to dosing, the drug product is thawed and sampled for cell number and viability to ensure the dose administered meets a pre-defined minimum.

We rely exclusively on the use of contract manufacturing organizations to manufacture our Lenti-D and LentiGlobin 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.

Future applications and opportunities

The investments that we have made to industrialize our gene therapy platform, processes and manufacturing may have application to other severe genetic and rare diseases. We believe that we have the opportunity to pursue other disease indications that would take advantage of our know-how and other intellectual property, and expertise in three main areas:

- Other lentiviral ex vivo applications with 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 hereditary diseases without the need for significant research work. In this way, we can move products efficiently through preclinical into clinical development. We may consider research and development programs targeting other monogenic, hereditary diseases that involve cells derived from HSCs. These programs may involve hereditary orphan diseases that could be developed and potentially commercialized on our own.

We also are pursuing gene therapy programs that target other cell types, such as T cells, that leverage the unique properties of lentiviral vectors. Through our global partnership with Celgene, we are now developing gene therapy products by inserting novel gene sequences into a patient's own T cells using lentiviral vectors for oncology. This represents a direct application of our expertise in gene therapy and our capabilities, know-how and patents associated with lentiviral gene therapy for ex vivo applications. As we further develop this program, we will investigate the opportunity to expand the application to other cell types for new potential indications.

· Lentiviral in vivo applications: 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, it opens up additional orphan and large market indications where this approach is more appropriate for the disease and targeted cells.

Strategic collaborations

Our objective is to develop and commercialize a next generation of products based on the transformative potential of gene therapy to treat patients with severe genetic diseases and cancer. To access the substantial funding and other resources required to develop and commercialize gene therapy products, we have formed, and intend to seek other opportunities to form, strategic alliances with collaborators who can augment our industry leading gene therapy expertise. To date, we have focused on forging a limited number of significant strategic alliances with leading pharmaceutical partners and academic laboratories where both parties contribute expertise to enable the discovery and development of potential gene therapy product candidates.

Our strategic alliance with Celgene

In March 2013, we announced a strategic collaboration with Celgene Corporation to discover, develop and commercialize novel disease-altering gene therapies in oncology. The collaboration focuses on applying gene therapy technology to genetically modify a patient's own T cells, to target and destroy cancer cells. Such modified T cells, which are called chimeric antigen receptor, or CAR T cells, have been shown to have beneficial effects in human clinical trials for patients with B cell lymphomas. The multi-year research and development collaboration has the potential to lead to the development and commercialization of multiple CAR T cell products. We are currently planning to advance the first CAR T product candidate from our collaboration with Celgene into clinical trials in early 2016.

Under the terms of the collaboration, for any product candidate selected for development under the collaboration, we are and will be responsible for conducting and funding all research and development activities performed up through completion of the initial Phase I clinical study, if any, of such product candidate. 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 completion of 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. If Celgene elects to exercise this option, it must pay us an option fee, subject to reduction if we elect to co-develop and co-promote that product candidate in the United States. In addition to the option fee, Celgene would also be obligated to pay us additional amounts based upon achievement of specified development and regulatory milestones and a percentage of net sales as a royalty, however, if we elect to co-develop and co-promote in the United States, this royalty only applies to sales outside the United States. The maximum option fee payable to us under these agreements, together with the maximum additional payments payable to us upon achievement of specified clinical, regulatory and commercial milestones, is $225 million, and the royalties payable to us range from the mid-single digits to mid-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.

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

payloads, plus a modest mark-up.

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, subject to a Celgene opt-in right to obtain a license to that product candidate, which right exists through a specified period following completion of a pivotal study for that product candidate.

We received an up-front payment of $75.0 million from Celgene in connection with the collaboration. The collaboration term ends in March 2016, unless extended at Celgene's option. Celgene may elect to extend the term twice, first for a period of two years and then for an additional period, in each case in consideration of a specified payment to us. Either party may terminate the agreement upon written notice to the other party in the event of the other party's uncured material breach. Celgene may terminate the agreement for any reason upon prior written notice to us. If the agreement is terminated, rights to product candidates in development at the time of such termination will be allocated to the parties through a mechanism included in the agreement. In addition, if Celgene terminates the agreement for our breach, any then- existing co-development and co-promotion agreement will be automatically terminated and

replaced with a license agreement for such product candidate and any amounts payable by Celgene under any then-existing product license agreements will be reduced.

Baylor College of Medicine

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

Call Option and Target Antigen License

During the initial three-year term of the collaboration and, if extended, during the first two-year extension term of the collaboration, in the event that we engage in a change in control transaction, including for such purposes a merger or consolidation of bluebird bio or the sale of all or substantially all of our assets, or if another person or entity or group of persons or entities acquires at least 50% of our voting capital stock, then Celgene has the right, but not the obligation, to terminate the collaboration agreement and obtain perpetual, non-terminable, worldwide, exclusive, fully paid-up licenses to all, but not less than all, of the product candidates previously identified under the collaboration agreement. We refer to this right to acquire such licenses as the call option.

Under the call option, the product candidates to which Celgene would have the right to acquire fully paid-up licenses include any product candidate previously licensed out of the collaboration during the term of the collaboration, any product candidate for which we have exercised our right to co-develop and co-promote the product candidate within the United States, any product candidate for which Celgene previously declined its option to obtain a license and any product candidate for which at least in vivo efficacy studies have been initiated or authorized by the JSC. The purchase price for such fully paid-up licenses would be determined pursuant to a binding arbitration process and would be paid on or about the consummation of the change in control transaction with our acquiror.

In addition, during the initial three-year term of the collaboration, but not during any extension of the collaboration agreement, in the event that we engage in a change in control transaction described above and Celgene exercises the call option described above, then, in addition to the right to acquire the fully paid-up licenses described above, Celgene would also have the right to obtain a perpetual, non-terminable, worldwide, exclusive license to our intellectual property to develop one or more CAR T cell products targeting one or more oncology associated target antigens identified by Celgene following the third anniversary of the collaboration agreement. There is no limit to the number of oncology associated target antigens Celgene may select under this license. Upon commercialization of any such product candidate so licensed by Celgene, Celgene would be obligated to pay us a specified milestone payment upon regulatory approval and a percentage of net sales as a royalty. We refer to this license agreement to develop one or more CAR T cell products targeting one or more oncology associated target antigens as the target antigen license.

The call option and the right to acquire a target antigen license may have the effect of delaying or preventing a change in control transaction involving us, or may reduce the number of companies interested in acquiring us. See “Item 1A. Risk Factors—Provisions in our collaboration agreement with Celgene Corporation may prevent or delay a change in control.”

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, 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, 2015, our patent portfolio includes the following:

- approximately 212 patents or patent applications that we own or have exclusively in-licensed from academic institutions and third parties related to lentiviral vectors and vector systems;
- approximately 66 patents or patent applications that we have non-exclusively in-licensed or optioned from academic institutions and third parties related to lentiviral vectors and vector systems;
- approximately 39 patents or patent applications that we own or have exclusively in-licensed from academic institutions and third parties, including eight that are co-owned with MIT, related to vector manufacturing or production;
- approximately eight patents or patent applications that have been non-exclusively in-licensed from academic institutions and third parties related to vector manufacturing or production;
- approximately 15 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from academic institutions and third parties related to therapeutic cellular products;
- approximately 31 patents or patent applications that we own or have exclusively in-licensed from academic institutions and third parties related to oncology products, including CAR T cell vector systems and manufacturing, T cell manufacturing, and therapeutic T cells; and
- approximately 46 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from academic institutions and third parties related to gene editing compositions and methods.

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

Childhood Cerebral Adrenoleukodystrophy (CCALD)

The CCALD platform includes three patent portfolios, described below.

- Pasteur Institute. The Pasteur patent portfolio contains patent applications directed to FLAP/cPPT elements and lentiviral vectors utilized to produce our Lenti-D product candidate for CCALD. As of January 31, 2015, we had an exclusive license (from Pasteur Institute) to eight issued U.S. patents and one pending U.S. application. Corresponding foreign patents and patent applications include pending applications or issued patents in Australia, Canada, China, Europe, Hong Kong, Israel, and Japan. We expect the issued composition of matter patents to expire from 2019-2023 in the United States, and from 2019-2020 in the rest of the world (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2019-2020 (excluding possible patent term extensions). We expect the patents and patent applications in this portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2019-2020 (worldwide, excluding possible patent term extensions).
- RDF. The in-licensed patent portfolio from Research Development Foundation, or RDF, in part, contains patents and patent applications directed to aspects of our lentiviral vectors utilized to produce our Lenti-D product candidate for CCALD. As of January 31, 2015, we had an exclusive license (from RDF) to seven issued U.S. patents and one pending U.S. application 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 2022-2023 (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 2021-2022 (excluding possible patent term extensions). We expect the patents and patent applications in this

portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2021-2022 (worldwide, excluding possible patent term extensions).

- bluebird bio. The bluebird bio patent portfolio contains patent applications directed to compositions of matter for CCALD 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, 2015, we owned one U.S. patent and two pending U.S. applications and 15 pending corresponding foreign applications or issued patents. We expect the issued composition of matter patents for CCALD gene therapy vectors to expire in 2032 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions). We

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

ß-thalassemia/SCD

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

- Pasteur Institute. The in-licensed Pasteur patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce our LentiGlobin product candidate for ß-thalassemia and SCD.
- 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 LentiGlobin product candidate for ß-thalassemia and SCD.
- MIT/bluebird bio. The co-owned patent portfolio contains patents and patent applications directed to certain specific compositions of matter for lentiviral ß-globin expression vectors. As of January 31, 2015, we co-owned one issued U.S. patent and one pending U.S. application, as well as corresponding foreign patents issued in Europe and Hong Kong. We expect the issued composition of matter patents to expire in 2023 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2023 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2023 (worldwide, excluding possible patent term extensions). We note that we have an exclusive license to MIT's interest in this co-owned intellectual property.

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

The lentiviral platform, which is potentially applicable to the CCALD, ß-thalassemia, SCD, 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/MIT. Another component of the bluebird bio patent portfolio includes the vector manufacturing platform and is potentially applicable to the CCALD, ß-thalassemia, SCD, oncology, and other programs. This portion of the portfolio contains patents and patent applications directed to compositions of matter for improved packaging cells and cell lines and improved methods for transfection and transduction of therapeutic cells. As of January 31, 2015, we owned two pending U.S. applications, 28 corresponding foreign patent applications; and one pending PCT application, which is due for national stage entry in February 2015. We expect composition of matter and method patents, if issued from a corresponding nonprovisional national stage application, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions). Note that we have an exclusive license to MIT's interest in this co-owned intellectual property.
- Oncology/CAR T cell platform (e.g., vectors, manufacturing, and cell therapy products)

The oncology/CAR T cell platform includes four patent portfolios, described below.

- Pasteur Institute. The Pasteur patent portfolio described above contains patents and patent applications that are applicable to our oncology platform.
- 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, 2015, we had an exclusive license (from RDF) to two pending U.S. applications related to our oncology platform. 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).

- CAR T Product Candidate License. We have in-licensed a patent portfolio that contains patents and patent applications directed to aspects of our oncology platform to produce lentiviral vectors for CAR T cell therapy product directed against B cell malignancies. As of January 31, 2015, we had a co-exclusive license to two issued U.S. patents and three pending U.S. applications. Corresponding foreign patents and patent applications related to our oncology platform include 13 pending applications and issued patents in New Zealand and South Africa. We expect the issued patents to expire in 2024 (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 2030 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2024-2030 (worldwide, excluding possible patent term extensions).

- bluebird bio. One aspect of the bluebird bio patent portfolio contains patents and patent applications directed to certain specific compositions of matter for generating CAR T cells. As of January 31, 2015, we owned five pending U.S. provisional applications and one pending PCT due for nationalization in June 2015. 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 2033-2035 (worldwide, excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2033-2035 (worldwide, excluding possible patent term extensions). Another component of the bluebird bio patent portfolio includes a T cell manufacturing platform and is applicable to the oncology program. This portion of the portfolio contains patents and patent applications directed to compositions of matter for improved T cell compositions and methods of making the same. As of January 31, 2015, we owned two pending U.S. provisional applications. We expect composition of matter and method patents, if issued from a corresponding nonprovisional application, and corresponding foreign applications if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2035 (worldwide, excluding possible patent term extensions).

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

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

- Pasteur Institute. The Pasteur patent portfolio described above may contain patents and patent applications that are potentially applicable to our genetic engineering 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 a patent portfolio that contains patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our ß-thalassemia, SCD, oncology, and other programs. As of January 31, 2015, we had an exclusive/co-exclusive license to two issued U.S. patents and three pending U.S. applications and 11 corresponding foreign 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 patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2030 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2030 (worldwide, excluding possible patent term extensions).
- Academic Gene Editing Licenses. We in-licensed a patent portfolio from an academic medical center containing patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our ß-thalassemia, SCD, oncology, and other programs. As of January 31, 2015, we had an exclusive license to two pending U.S. applications and 19 corresponding pending foreign patent applications related to our gene editing platform. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2032-2033(excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2032-2033 (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 ß-thalassemia, SCD, oncology, and other programs. As of January 31, 2015, we co-owned (with Cellectis) two pending PCT applications, both due for nationalization November 2015. We expect any composition of matter or methods patents, if issued from a corresponding 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 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 new drug application, or NDA, 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 contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors 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. This agreement was amended once in 2012 and again in 2013. Inserm-Transfert is referred to herein as Inserm. The Inserm licensed patent portfolio includes at least three U.S. and foreign patents and patent applications. This portfolio has no pending applications. Inserm retains the right to practice the intellectual property licensed under the agreement for educational, clinical and preclinical studies purposes.

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

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

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

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

2016.

Institut Pasteur

In September 2011, we 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 in a range of indications. This agreement was amended twice in 2012 and a third time in 2013. The Institut Pasteur licensed patent portfolio includes at least 23 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 (HIV-1 and HIV-2) lentiviral vector and non-exclusive for products containing non-human lentiviral vector. 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. If we receive any income (cash or non-cash) in connection with such sublicenses for products targeting indications other than ALD (including CCALD and AMN), or -hemoglobinopathies (including -thalassemia, and SCD), we must pay Institut Pasteur a percentage of such income varying from low single digits to lower to mid double digits depending on the nature of the sublicense.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our Lenti-D and LentiGlobin 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 day 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. 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, non-clinical 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 26 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2023. This license also has been amended to include a case jointly owned by MIT and us wherein we received the exclusive license to MIT's rights in this case. MIT retains the right to practice the intellectual property licensed under the agreement for noncommercial research purposes.

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

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our LentiGlobin product candidate, we will be obligated to pay MIT a percentage of net sales by us or our sublicensees as a royalty. This royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than

a specified percentage that is less than one-percent. In addition, we make under this agreement an annual maintenance payment which may be credited against the royalty payments.

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

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

Research Development Foundation

In December 2011, we entered into an exclusive license with RDF to use certain patents that involve lentiviral vectors. The RDF licensed patent portfolio includes at least 14 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 of 2021 or 2022. 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 2023.

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 and Lenti-D product candidates, if approved and our preclinical CAR T product candidates. These efforts include the following:

·CCALD: The current standard of care for the treatment of CCALD 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.

- ß-thalassemia: The current standard of care for the treatment of ß-thalassemia in the developed world is chronic blood transfusions to address the patient's anemia. In addition, such patients often receive iron chelation therapy to help manage the iron overload associated with their chronic blood transfusions. We understand that established biopharmaceutical companies, such as Novartis AG and ApoPharma Inc., who provide the leading iron chelation therapy, are seeking to develop improvements to their product profile and accessibility. In addition, some patients with ß-thalassemia receive HCST treatment, particularly if a sufficiently well-matched source of donor cells is identified. We understand that various academic centers around the world are seeking to develop improvements to allogeneic HSCT. A number of different approaches are under investigation to improve treatment options, including iron modulating agents and fetal hemoglobin regulators. There are also several different groups developing gene therapy approaches for ß-thalassemia. Some of these groups use a similar ex vivo autologous approach, but make use of different vectors and different cell processing techniques. These include: Memorial Sloan Kettering, which received clearance for its IND from the FDA in 2012 for a Phase I/II gene therapy study; GlaxoSmithKline Plc, which has entered into an agreement with the San Raffaele Telethon Institute for Gene Therapy to advance several gene therapy programs, including one for ß-thalassemia; Sangamo BioSciences Inc., through its partnership with Biogen Idec, which has announced plans to initiate a Phase I clinical study using zinc finger nuclease-mediated gene-correction techniques in hemoglobinopathies including ß-thalassemia and Acceleron Pharma, Inc., which is investigating Sotatercept, a protein therapeutic that targets TGF- , in a Phase II clinical trial in subjects with ß-thalassemia.
- Sickle cell disease: The current standard of care for the treatment of SCD in the developed world is chronic blood transfusions or hydroxyurea (a generic drug). In addition, such patients often receive iron chelation therapy to help manage the iron overload associated with chronic blood transfusions. We are aware of ongoing studies that continue to evaluate the efficacy and safety of hydroxyurea in various populations. In addition, some patients with SCD receive allogeneic HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. We understand that various academic centers around the world are seeking to develop improvements to allogeneic HSCT. A number of different therapeutic approaches are under investigation targeting the various aspects of SCD pathophysiology, including: fetal hemoglobin regulators, including HQK-1001 in Phase II studies supported by HemaQuest Pharmaceuticals Inc., and Vorinostat in Phase II studies supported by Merck & Co.; and 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). 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/II gene therapy study for SCD, although to our knowledge no clinical studies have been initiated and Sangamo BioSciences Inc., through its partnership with Biogen Idec, which has announced plans to investigate the use of zinc finger nuclease-mediated gene-correction techniques in hemoglobinopathies including SCD, although to our knowledge no clinical studies have been initiated.
- CAR T therapies for oncology: A number of pharmaceutical companies and academic collaborators are researching and developing CAR T therapies for oncology, including Novartis AG in collaboration with the University of Pennsylvania, Juno Therapeutics, Inc., in collaboration with Memorial Sloan Kettering and the Fred Hutchinson Cancer Research Center, Kite Pharma, Inc. in collaboration with Amgen, Inc. and the National Institutes of Health, among others. Many of the CAR T programs being developed by these companies are already in Phase I/II clinical trials for multiple indications.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. Accordingly, our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, or more effectively

marketed and sold, than any treatment we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our treatments.

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

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

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over competitive generic products.

Government regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. FDA approval must be obtained before clinical testing of biological products, and each clinical study protocol for a gene therapy product is reviewed by the FDA and, in some instances, the NIH, through its RAC. FDA approval also must be obtained before marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the CBER regulates gene therapy products. The CBER works closely with the NIH and its RAC, which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in gene therapy INDs.

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

U.S. biological products development process

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

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical studies may begin;
- performance of adequate and well-controlled human clinical studies according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its

intended use;

- submission to the FDA of a Biologics License Application, or BLA, for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with GMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or GTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry,

toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation is submitted to and the study is registered with the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, however many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee, that discusses protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OBA web site and may be accessed by the public.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

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

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

· Phase I. The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
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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 and the FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

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

U.S. review and approval processes

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

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed

product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with GMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the GTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the

GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure GMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

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

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

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

Orphan drug designation

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

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan

product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited development and review programs

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

the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Under the Breakthrough Therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, Breakthrough Therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Post-approval requirements

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

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or

withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

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

U.S. patent term restoration and marketing exclusivity

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

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

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

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

Additional regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws

and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

U.S. Foreign Corrupt Practices Act

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

Government regulation outside of the United States

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

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

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

To obtain regulatory approval of an investigational biological product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements. The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, new chemical entities generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

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

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

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;

- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

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

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

Employees

As of January 31, 2015, we had 143 full-time employees, 41 of whom have Ph.D., M.D. or Pharm.D. degrees. Of these full-time employees, 112 employees are engaged in research and development activities and 31 employees are engaged in finance, legal, business development, human resources, information technology, facilities and general administrative functions. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relations with our employees to be good.

Corporate Information

We were incorporated in Delaware in April 1992 under the name Genetix Pharmaceuticals, Inc., and subsequently changed our name to bluebird bio, Inc. in September 2010. Our mailing address and executive offices are located at 150 Second Street, Third Floor, Cambridge, Massachusetts and our telephone number at that address is (339) 499-9300. We maintain an Internet website at the following address: www.bluebirdbio.com. The information on our website is not incorporated by reference in this annual report on Form 10-K or in any other filings we make with the Securities and Exchange Commission, or SEC.

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

Item 1A. Risk Factors

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

Risks related to the discovery and development of our product candidates

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

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

In addition, the clinical study requirements of the FDA, the EMA and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or extensively studied pharmaceutical or other product candidates. At the moment, only one gene therapy product, UniQure’s Glybera, which received marketing authorization in the EU in 2012, has been approved in the Western world, which makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, the EU or other jurisdictions. Approvals by the EMA and the European Commission may not be indicative of what the FDA may require for approval.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. For example, the FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical studies conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health, or the NIH, are also subject to review by the NIH Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or the RAC. Although the FDA decides whether individual gene therapy protocols may proceed, the RAC review process can impede the initiation of a clinical study, even if the FDA has reviewed the study and approved its initiation. Conversely, the FDA can put an investigational new drug application, or IND, on clinical hold even if the RAC has provided a favorable review. Also, before a clinical study can begin at an NIH-funded institution, that institution's institutional review board, or IRB, and its Institutional Biosafety Committee will have to review the proposed clinical study to assess the safety of the study. In addition, serious adverse events or developments in clinical trials of gene therapy product candidates conducted by others may cause the FDA or other regulatory bodies to initiate a clinical hold on our clinical trials or otherwise change the requirements for approval of any of our product candidates.

These regulatory review agencies, committees and advisory groups and the new requirements and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these

regulatory and advisory groups and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

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

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

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

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

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

Our current product candidates are being developed to treat rare conditions and certain cancers. We plan to seek initial marketing approval in the United States and the European Union. We may not be able to initiate or continue clinical studies if we cannot enroll a sufficient number of eligible patients to participate in the clinical studies required by the

FDA or the EMA or other regulatory agencies. Our ability to successfully initiate, enroll and complete a clinical study in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

·difficulty in establishing or managing relationships with contract research organizations, or CROs, and physicians;
·different standards for the conduct of clinical studies;
·our inability to locate qualified local consultants, physicians and partners; and

- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

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

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

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

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

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

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

- be delayed in obtaining regulatory approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be required to perform additional clinical studies or clinical studies of longer duration to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its use;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or

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·experience damage to our reputation.

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

We have not completed any clinical studies of our current viral vectors or product candidates derived from these viral vectors. Success in early clinical studies may not be indicative of results obtained in later studies.

Our current viral vectors and our product candidates first initiated evaluation in human clinical studies in 2013, and we may experience unexpected results in the future. Earlier gene therapy clinical studies, which we believe serve as proof-of-concept for our product candidates, utilized lentiviral vectors similar to ours. However, these studies should not be relied upon as evidence that our future clinical studies will succeed. Study designs and results from previous studies are not necessarily predictive of our future clinical study designs or results, and initial results may not be confirmed upon full analysis of the complete study data. Our product candidates may also fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical studies.

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

Initial success in our ongoing clinical studies may not be indicative of results obtained when these studies are completed.

In December 2014, at the Annual Meeting of the American Society of Hematology (ASH), we announced data from the first eight subjects treated with LentiGlobin BB305 drug product. In the first four subjects, each of whom had at least three months of follow up, treatment with LentiGlobin BB305 drug product resulted in sufficient hemoglobin production to reduce or eliminate the need for transfusion support among patients with ß -thalassemia major who would otherwise require chronic blood transfusions. These data include the first five subjects treated in the Northstar Study and the first three subjects from the HGB-205 Study. Although the initial clinical data on these subjects are encouraging, the data are preliminary in nature, based on limited periods of time since patient infusion, and the Northstar and HGB-205 Studies are not complete. There is limited data concerning long-term safety and efficacy following treatment with LentiGlobin drug product. These data, or other positive data, may not continue or occur for these subjects or for any future subjects in this study, and may not be repeated or observed in ongoing or future studies involving our LentiGlobin product candidate, including the HGB-205 Study, the Northstar Study or the HGB-206 Study in severe SCD. There can be no assurance that subjects for whom periodic transfusion support has been reduced or temporarily eliminated will not receive transfusion support in the future. Furthermore, there can be no assurance that any of these studies will ultimately be successful or support further clinical advancement of this product candidate. There is a high failure rate for drugs and biologics proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies, and any such setbacks in our clinical development could have a material adverse effect on our business and operating results.

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

The FDA has advised us that our Starbeam Study, which is a single-arm, open-label study to evaluate the safety and efficacy of our Lenti-D product candidate to halt the progression of CCALD, may not be deemed to be a pivotal study or may not provide sufficient support for a Biologics License Application, or BLA, submission. The FDA normally requires two pivotal clinical studies to approve a drug or biologic product, and thus the FDA may require that we conduct additional clinical studies of Lenti-D prior to a BLA submission. The FDA typically does not consider a single clinical study to be adequate to serve as a pivotal study unless it is, among other things, well-controlled and demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, and a confirmatory study would be practically or ethically impossible. Due to the nature of CCALD and the limited number of patients with this condition, a placebo-controlled and blinded study is not practicable for ethical and other reasons. However, it is still possible that, even if we achieve favorable results in the Starbeam Study, the FDA may require us to enroll additional subjects or conduct additional clinical studies, possibly involving a larger sample size or a different clinical study design, particularly if the FDA does not find the results from the Starbeam Study to be sufficiently persuasive to support a BLA

submission. The FDA may also require that we conduct a longer follow-up period of subjects treated with our Lenti-D product candidate prior to accepting our BLA submission.

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

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

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

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

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

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

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

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical studies, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory advisory group or authority recommends non-approval or restrictions on approval. In

addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical studies and the review process. Regulatory agencies also may approve a treatment candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our treatment candidates. For example, the development of our product candidates for pediatric use is an important part of our current business strategy, and if we are unable to obtain regulatory approval for the desired age ranges, our business may suffer.

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

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

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with good manufacturing practices, or GMP, and adherence to commitments made in the BLA. If we or a regulatory agency discovers previously unknown problems with a product such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

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

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

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

Risks related to our reliance on third parties

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

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

quality control protocols utilized in certain commercial settings.

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

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in

completing, the preclinical and clinical studies required to support future IND and BLA submissions and approval of our product candidates.

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

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

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

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

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

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

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Some components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with GMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA or MAA on a timely basis and where required, must adhere to the FDA's or other regulator's good laboratory practices, or GLP, and GMP regulations enforced by the FDA or other regulator through facilities inspection programs. Some of our contract manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA or other regulatory approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA or other regulatory approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable

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

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

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. The number of manufacturers with the necessary manufacturing capabilities is limited. In addition, an alternative manufacturer would need to be qualified through a BLA supplement or similar regulatory submission which could result in further delay. The

regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

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

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

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

We and our CROs are required to comply with the FDA's GCPs for conducting, recording and reporting the results of clinical studies to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical study participants are protected. The FDA enforces these GCPs through periodic inspections of study sponsors, principal investigators and clinical study sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical studies may be deemed unreliable and the FDA may require us to perform additional clinical studies before approving any marketing applications. Upon inspection, the FDA may determine that our clinical studies did not comply with GCPs. In addition, our future clinical studies will require a sufficient number of test subjects to evaluate the safety and efficacy of our product candidates. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical studies, which would delay the regulatory approval process.

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

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

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

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

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights

with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks related to our financial condition and capital requirements

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

We are a clinical-stage biotechnology company, and we have not yet generated significant revenues. We have incurred net losses in each year since our inception in 1992, including net losses of $48.7 million and $25.3 million for the years ended December 31, 2014 and 2013, respectively. As of December 31, 2014, we had an accumulated deficit of $147.4 million.

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

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

- continue our research and preclinical and clinical development of our product candidates;
- expand the scope of our current clinical studies for our product candidates;
- initiate additional preclinical, clinical or other studies for our product candidates, including under our collaboration agreement with Celgene;
- further develop the manufacturing process for our vectors or our product candidates;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;
- seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- make milestone or other payments under any license agreements or our stock purchase agreement with the former equityholders of Pregenen;
- maintain, protect and expand our intellectual property portfolio;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- attract and retain skilled personnel;
- build additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above.

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

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

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

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

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

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

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

As of December 31, 2014, our cash, cash equivalents and marketable securities were $492.0 million. We expect that our existing cash and cash equivalents will be sufficient to fund our current operations through 2017. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic

objectives.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree

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

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

Risks related to commercialization of our product candidates

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

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

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

Additionally, since the HSCs have a limited window of stability following extraction from the patient, we must set up transduction facilities in the regions where we wish to commercialize our product. Currently, we rely on third-party contract manufacturers in the United States and Europe to produce our product candidates for our clinical studies. Since a portion of our target patient populations will be outside the United States and Europe, we will need to set up additional transduction facilities that can replicate our transduction process. Establishment of such facilities may be financially impractical or impeded by technical, quality, or regulatory issues related to these new sites and we may also run into technical or scientific issues related to transfer of our transduction process or other developmental issues that we may be unable to resolve in a timely manner or with available funds.

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

In addition, any significant disruption in our supplier relationships could harm our business. We source key materials from third parties, either directly through agreements with suppliers or indirectly through our manufacturers who have

agreements with suppliers. There are a small number of suppliers for certain key materials that are used to manufacture our product candidates. Such suppliers may not sell these key materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these key materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these key materials.

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

We have no experience selling and marketing our product candidates. To successfully commercialize any products that may result from our development programs, we will need to develop these capabilities, either on our own or with others. We may enter into collaborations with other entities to utilize their mature marketing and distribution capabilities, but we may be unable to enter into marketing agreements on favorable terms, if at all. If our future collaborative partners do not commit sufficient resources to commercialize our future products, if any, and we are unable to develop the necessary marketing capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We will be competing with many companies that currently have

extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

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

We are engaged in gene therapy and in the field of CAR T cells in oncology, both of which are competitive and rapidly changing fields. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Some of the pharmaceutical and biotechnology companies we expect to compete with include GlaxoSmithKline plc through their collaboration with TIGET/MolMed, Sangamo BioSciences Inc. through their collaboration with Biogen Idec, Merck & Co., Inc., Novartis AG through their collaboration with the University of Pennsylvania, GlycoMimetics Inc., Acceleron Pharma, Inc., Kite Pharma, Inc., Pfizer Inc. through their collaboration with Cellectis SA, Adaptimmune Inc. and Juno Therapeutics. In addition, many universities and private and public research institutes are active in our target disease areas.

Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, products that are more effective or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization and market penetration than us. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars due to the changing regulatory environment. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be “highly similar,” or biosimilar, to or “interchangeable” with an FDA-approved biological product. This new pathway could allow competitors to reference data from biological products already approved after 12 years from the time of approval. In his proposed budget for fiscal year 2014, President Obama proposed to cut this 12-year period of exclusivity down to seven years. He also proposed to prohibit additional periods of exclusivity due to minor changes in product formulations, a practice often referred to as “evergreening.” In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data from biological products already approved, but will not be able to get on the market until 10 years after the time of approval. This 10-year period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products. If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences. Expiration or successful challenge of our applicable patent rights could also trigger competition from other products, assuming any relevant exclusivity period has expired.

In addition, although our product candidates have been granted orphan drug status by the FDA and EMA, there are limitations to the exclusivity. In the United States, the exclusivity period for orphan drugs is seven years, while pediatric exclusivity adds six months to any existing patents or exclusivity periods. In Europe, orphan drugs may be able to obtain 10 years of marketing exclusivity and up to an additional two years on the basis of qualifying pediatric

studies. However, orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria. Additionally, a marketing authorization holder may lose its orphan exclusivity if it consents to a second orphan drug application or cannot supply enough drug. Orphan drug exclusivity also can be lost when a second applicant demonstrates its drug is “clinically superior” to the original orphan drug.

Finally, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors’ products. The availability of our competitors’ products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

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

Ethical, social and legal concerns about gene therapy and genetic research could result in additional regulations restricting or prohibiting the products and processes we may use. Even with the requisite approvals, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party or governmental payors accepting gene therapy products in general, and our product candidates in particular, as medically useful, cost-effective, and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. If

these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

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

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

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

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

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights;
- economic weakness, including inflation, or political instability in particular foreign economies and markets; and
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country.

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

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

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products, including gene therapies. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what

CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United

States and have not been approved for reimbursement in certain European countries. In addition, costs or difficulties associated with the reimbursement of Glybera could create an adverse environment for reimbursement of other gene therapies.

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

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

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

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

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

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

Risks related to our business operations

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

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

- diversion of managerial resources from day-to-day operations;
- challenges associated with integrating acquired technologies and operations of acquired companies;
- exposure to unforeseen liabilities;
- difficulties in the assimilation of different cultures and practices, as well as in the assimilation and retention of broad and geographically dispersed personnel and operations;
- misjudgment with respect to value, return on investment or strategic fit;
- higher than expected transaction costs; and

·additional dilution to our existing stockholders if we issue equity securities as consideration for any acquisitions.

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

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

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

On June 30, 2014, we acquired all of the outstanding capital stock of Precision Genome Engineering, Inc., or Pregenen. Based in Seattle, Washington, Pregenen is focused on the development of gene editing and cell signaling technologies. The success of our acquisition of Pregenen will depend, in part, on our ability to successfully integrate Pregenen's business and operations and fully realize the anticipated benefits and synergies from combining our business with Pregenen's business, in particular our ability to advance Pregenen's gene editing and cell signaling technologies to the stage where they can be incorporated into our existing or new product candidates. However, to realize these anticipated benefits, we must successfully combine these businesses and continue the research and development activities previously undertaken by Pregenen as a stand-alone company. If we are unable to achieve these objectives, the anticipated benefits of our acquisition of Pregenen may not be realized fully or at all or may take longer to realize than expected. Any failure to timely realize these anticipated benefits could have a material adverse effect on our development programs, expenses and operating results.

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

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

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

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

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

As of January 31, 2015, we had 143 full-time employees. As our business, research and development activities expand and as we continue the activities required under our collaboration with Celgene, we expect to expand our full-time employee base and to hire more consultants and contractors. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA and non-U.S. regulators, provide accurate information to the FDA and non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical studies, which could result in regulatory sanctions and cause serious harm to our reputation or could cause regulatory agencies not to approve our product candidates. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

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

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

- impairment of our business reputation;
- withdrawal of clinical study participants;
- costs due to related litigation;
- distraction of management’s attention from our primary business;

· substantial monetary awards to patients or other claimants;
· the inability to commercialize our product candidates; and
· decreased demand for our product candidates, if approved for commercial sale.

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

brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

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

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

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

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

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

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our gene therapy and gene editing platforms. Although our Lenti-D and LentiGlobin product candidates are currently in clinical development, our research programs, including those subject to our collaboration with Celgene, may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

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

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

of success.

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

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

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

On December 31, 2014, we ceased to be an “emerging growth company,” and the reduced disclosure requirements applicable to emerging growth companies no longer apply to us.

On December 31, 2014, we ceased to be an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, and the reduced disclosure requirements applicable to emerging growth companies no longer apply to us. As a large accelerated filer, we are now subject to certain disclosure requirements that are applicable to other public companies that have not been applicable to us as an emerging growth company. These requirements include:

- compliance with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- compliance with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements;
- full disclosure obligations regarding executive compensation; and
- compliance with the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

Risks related to our intellectual property

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

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

If the patent applications we hold or have in-licensed with respect to our programs or product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. Several patent applications covering our product candidates have been filed recently. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available however the life of a patent, and the protection it affords, is limited. Even if

patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

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

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

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

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

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

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods

for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

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

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

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

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

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

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

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

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

In many cases, patent prosecution of our licensed technology is controlled solely by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution,

we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

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

·the priority of invention of patented technology.

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

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

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

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

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

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

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The U.S. PTO is currently developing regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, were enacted March 16, 2013. However, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

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

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of others in their work

for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We have had in the past, and we may also have to in the future, ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to

use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

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

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

If we or one of our licensing partners initiated legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

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

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore obtaining and enforcing biotechnology patents is costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken

our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents,

trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks related to ownership of our common stock

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

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

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

- adverse results or delays in preclinical or clinical studies;
- reports of adverse events in other gene therapy products or clinical studies of such products;
- inability to obtain additional funding;
- any delay in filing an IND or BLA for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA's review of that IND or BLA;
- failure to develop successfully and commercialize our product candidates;
- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic collaboration partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

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

In accordance with the guidelines specified under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, and our policies regarding stock transactions, a number of our employees, including executive officers, have adopted and may continue to adopt stock trading plans pursuant to which they have arranged to sell shares of our common stock from time to time in the future. Generally, sales under such plans by our executive officers and directors require public filings. Actual or potential sales of our common stock by such persons could cause the price of our common stock to fall or prevent it from increasing for numerous reasons. For example, a substantial number of shares of our common stock becoming available (or being perceived to become available) for sale in the public market could cause the market price of our common stock to fall or prevent it from increasing. Also, actual or potential sales by such persons could be viewed negatively by other investors.

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

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

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

We could be subject to securities class action litigation.

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

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

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. We have completed several financings since our inception which we believe have resulted in a change in control as defined by IRC Section 382. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a

result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

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

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

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

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

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

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

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

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

Provisions in our collaboration agreement with Celgene Corporation may prevent or delay a change in control.

Our collaboration agreement with Celgene Corporation provides that during the initial three-year term of the collaboration and, if extended, during the first extension term of the collaboration which is two years, in the event that we engage in a change in control transaction, including for such purposes a merger or consolidation of bluebird bio or the sale of all or substantially all of our assets, or if another person or entity or group of persons or entities acquires at least 50% of our voting capital stock, then Celgene has the right, but not the obligation, to terminate the collaboration agreement and obtain perpetual, non-terminable, worldwide, exclusive, fully paid-up licenses to all, but not less than all, of the product candidates previously identified under the collaboration agreement. We refer to this right to acquire such licenses as the call option.

Under the call option, the product candidates to which Celgene would have the right to acquire fully paid-up licenses include any product candidate previously licensed out of the collaboration during the term of the collaboration, any product candidate for which we have exercised our right to co-develop and co-promote the product candidate within the United States, any product candidate for which Celgene previously declined its option to obtain a license and any product candidate for which at least in vivo efficacy studies have been initiated or authorized by the joint steering

committee for the collaboration. The purchase price for such fully paid-up licenses would be determined pursuant to a binding arbitration process and would be paid on or about the consummation of the change of control transaction with our acquiror. The call option will lapse at the end of the three-year term of the collaboration, unless extended, in which case it will lapse at the end of the first extension term, which is two years, even if the collaboration is extended further.

In addition, during the initial three-year term of the collaboration, but not during any extension of the collaboration agreement, in the event that we engage in a change in control transaction described above and Celgene exercises the call option described above, then, in addition to the right to acquire the fully paid-up licenses described above, Celgene would also have the right to obtain a perpetual, non-terminable, worldwide, exclusive license to our intellectual property to develop one or more CAR T cell products targeting one or more oncology associated target antigens identified by Celgene following the third anniversary of the collaboration agreement. There is no limit to the number of oncology associated target antigens Celgene may select under this license. Upon commercialization of any such product candidate so licensed by Celgene, Celgene would be obligated to pay us a specified milestone payment upon regulatory approval and a percentage of net sales as a royalty. We refer to this license agreement to develop one or more CAR T cell products targeting one or more oncology associated target antigens as the target antigen license. The right to acquire a target antigen license will lapse after the initial three-year term of the collaboration, even if the collaboration is extended.

The call option and the right to acquire a target antigen license may have the effect of delaying or preventing a change in control transaction involving us, or may reduce the number of companies interested in acquiring us. If Celgene were to exercise the call option, it would gain exclusive development and marketing rights to the product candidates developed under the collaboration agreement, including any product for which we previously exercised our co-development and co-promotion rights. Were this to happen, our successor would not receive a royalty on net sales of any of the products out-licensed in connection with the call option, nor would it realize any value it may otherwise ascribe to our right to co-develop and co-promote within the United States any products developed during the collaboration. Moreover, if such event were to occur during the first three years of the collaboration, Celgene would also effectively have the exclusive right to develop and market an unlimited number of additional CAR T cell products using our gene therapy platform, whether or not these products were first identified or developed during the course of the collaboration, which product candidates would target a list of oncology associated target antigens that would not be known at the time we close our change in control transaction. This license could potentially give Celgene rights to our gene therapy platform for CAR T cell product candidates in the event we are acquired prior to the third anniversary of the collaboration.

These provisions could have the effect of delaying or preventing a change in control transaction involving bluebird bio, or could reduce the number of companies interested in acquiring us, in particular during the first three years of the collaboration. This risk may become particularly acute in the event either of our lead product candidates, Lenti-D or LentiGlobin, suffer material setbacks or delays in their clinical advancement, as a result of which the long-term strategic value potential acquirors may ascribe to us could increasingly be attributable to the potential long-term value of any CAR T cell products we develop under the collaboration.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our corporate headquarters are located in Cambridge, Massachusetts. Our current leased facility encompasses approximately 53,400 square feet of office and laboratory space, located at 150 Second Street, Cambridge,

Massachusetts. The nine-year lease commenced on January 1, 2014. We have the option to extend this lease by an additional five years. We also lease our former corporate headquarters in Cambridge, Massachusetts, which lease expires on March 31, 2015, but we have fully subleased our former corporate headquarters through March 31, 2015. We also lease approximately 3,900 square feet of office and laboratory space in Seattle, Washington, which lease expires in December 2016. We believe that our existing facilities are adequate for our current needs. As additional space is needed in the future, we believe that suitable space will be available in the required locations on commercially reasonable terms.

Item 3. Legal Proceedings

In the ordinary course of business, we are from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation relating to intellectual property, commercial arrangements and other matters. While the outcome of these proceedings and claims cannot be predicted with certainty, as of December 31, 2014, we were not party to any legal or arbitration proceedings that may have, or have had in the recent past, significant effects on our financial position or profitability. No governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Our common stock has been traded on the Nasdaq Global Select Market under the symbol "BLUE" since our initial public offering on June 19, 2013. Prior to this time, there was no public market for our common stock. The following table shows the high and low sale prices per share of our common stock as reported on the Nasdaq Global Select Market for the periods indicated:

	High	Low
2013		
Second Quarter 2013 (beginning June 19, 2013)	$26.91	$24.97
Third Quarter 2013	$35.00	$24.43
Fourth Quarter 2013	$27.11	$17.53
2014		
First Quarter 2014	$28.08	$19.34
Second Quarter 2014	$41.75	$17.40
Third Quarter 2014	$40.31	$30.33
Fourth Quarter 2014	$94.77	$29.73

On February 18, 2015, the last reported sale price for our common stock on the Nasdaq Global Select Market was $91.89 per share.

Stock Performance Graph

The graph set forth below compares the cumulative total stockholder return on our common stock between June 19, 2013 (the date of our initial public offering) and December 31, 2014, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of $100 on June 19, 2013 in our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any. The graph assumes our closing sales price on June 19, 2013 of $26.91 per share as the initial value of our common stock and not the initial offering price to the public of $17.00 per share.

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

Holders

As of February 18, 2015, there were approximately 22 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

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

Securities authorized for issuance under equity compensation plans

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

Purchases of Equity Securities by the Issuer or Affiliated Purchasers

There were no repurchases of shares of common stock made during the year ended December 31, 2014.

Item 6. Selected Financial Data

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

We derived the consolidated financial data for the years ended December 31, 2014, 2013 and 2012 and as of December 31, 2014 and 2013 from our audited consolidated financial statements, which are included elsewhere in this Annual Report on Form 10-K. We derived the consolidated financial data for the year ended December 31, 2011 and as of December 31, 2012 and 2011 from our audited consolidated financial statements that are not included elsewhere in this Annual Report on Form 10-K. Historical results are not necessarily indicative of the results to be expected in future periods.

	Years Ended December 31,			
	2014	2013	2012	2011
	(1)			
	(in thousands, except per share amounts)			
Consolidated statements of operations data:				
Revenue:				
Collaboration revenue	$25,031	$19,792	$—	$—
Research and license fees	390	389	340	640
Grant revenue	—	—	—	242
Total revenue	25,421	20,181	340	882
Expenses:				
Research and development	62,574	31,002	17,210	11,409
General and administrative	23,227	14,126	6,846	4,615
Change in fair value of contingent consideration	246	—	—	—
Total operating expenses	86,047	45,128	24,056	16,024
Loss from operations	(60,626)	(24,947)	(23,716)	(15,142)
Other income (expense), net	120	(374)	46	(456)
Benefit from income taxes	11,797	—	—	—
Net loss	$(48,709)	$(25,321)	$(23,670)	$(15,598)
Net loss per share applicable to common stockholders - basic and diluted	$(1.83)	$(2.02)	$(13.79)	$(171.59)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	26,546	12,555	262	120

	As of December 31,			
	2014	2013	2012	2011
	(1)			

	(in thousands)			
Consolidated balance sheet data:				
Cash and cash equivalents	$347,845	$206,279	$67,011	$25,604
Marketable securities	144,158	-	-	3,507
Working capital	437,011	177,113	63,156	27,087
Total assets	556,739	224,390	69,322	30,918
Contingent consideration, net of current portion	6,321	—	—	—
Preferred stock	—	—	122,177	82,403
Common stock and additional paid-in capital	638,712	250,342	15,270	7,734
Total stockholders' equity (deficit)	491,257	151,667	(55,747)	(55,707)

(1) Starting in 2014, the selected financial data includes the impact of the acquisition of Pregenen in June 2014. See Note 12. “Business Combinations” in the accompanying notes to consolidated financial statements for additional information.

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

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

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

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

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

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

Overview

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

We are conducting a Phase II/III clinical study, called the Starbeam Study, of our most advanced product candidate, Lenti-D, to evaluate its safety and efficacy in subjects with childhood cerebral adrenoleukodystrophy, or CCALD, a rare, hereditary neurological disorder affecting young boys that is often fatal. In October 2013, we announced that the first subject had been treated in this study. We are also planning to conduct an observational study of subjects with CCALD treated by allogeneic hematopoietic stem-cell transplant referred to as the ALD-103 study.

We are also conducting two Phase I/II clinical studies of our next most advanced product candidate, LentiGlobin, to evaluate its safety and efficacy in subjects with ß-thalassemia major, a hereditary blood disorder that often leads to severe anemia and shortened lifespans. In December 2013, we announced that the first subject with ß-thalassemia major had been treated in our European study of LentiGlobin, called the HGB-205 study, which also permits the enrollment of subjects with severe sickle cell disease, or SCD. In October 2014 we announced that the first subject

with severe SCD had been treated in the European HGB-205 study. In March 2014, we announced that the first subject with ß-thalassemia major had been treated in our other study of LentiGlobin being conducted in the United States, Australia and Thailand, called the Northstar Study. We presented results from the HGB-205 study at the European Hematology Association Congress in June 2014 and presented results from both the Northstar Study and HGB-205 study at the American Society of Hematology Annual Meeting in December 2014.

We have initiated a Phase I clinical study in the United States, called the HGB-206 Study, to evaluate the safety and efficacy of LentiGlobin in subjects with severe SCD.

In March 2013, we announced a global strategic collaboration with Celgene Corporation, or Celgene, to discover, develop and commercialize chimeric antigen receptor-modified T cells, or CAR T cells, as potentially disease-altering therapies in oncology. This collaboration has an initial term of three years, and Celgene has made a $75.0 million up-front, non-refundable cash payment to us as consideration for entering into the collaboration. During the year ended December 31, 2014, we recognized $25.0 million of revenue associated with our collaboration with Celgene related to the research and development services performed. As of December 31, 2014, we have classified $30.7 million of deferred revenue related to our collaboration with Celgene as current or long-term in the accompanying balance sheets based on the contractual term of the arrangement. We expect the first product candidate from this collaboration to enter clinical trials in early 2016.

In June 2014, we acquired Precision Genome Engineering, Inc., or Pregenen, a privately-held biotechnology company headquartered in Seattle, Washington. Through the acquisition, we obtained rights to Pregenen's gene editing and cell signaling technology. Under the terms of the agreement, we paid the former Pregenen equityholders $5.1 million in cash and issued 405,400 shares of our common stock with a fair value of $15.6 million. The consideration for the transaction also includes an additional 94,117 shares of our common stock that will be held for a period of 18 months after the acquisition and may be used to settle certain claims for indemnification for breaches or inaccuracies in Pregenen's representations and warranties, covenants, and agreements. Additionally, the total consideration was subject to post-closing adjustments relating to the working capital of Pregenen as of closing, and we issued an additional 2,119 shares with a fair value of $0.1 million in July 2014. The agreement also provides for up to $135.0 million in future contingent cash payments by us upon the achievement of certain preclinical, clinical and commercial milestones related to the Pregenen technology, of which $15.0 million relates to preclinical milestones, $20.1 million relates to clinical milestones and $99.9 million relates to commercial milestones. We estimate these future contingent cash payments have a fair value of $6.8 million as of December 31, 2014.

As of December 31, 2014, we had cash, cash equivalents and marketable securities of approximately $492.0 million. We expect cash, cash equivalents and marketable securities to fund operations through 2017.

Since our inception in 1992, we have devoted substantially all of our resources to research and development efforts relating to our product candidates, including activities to manufacture product candidates, to conduct clinical studies of our product candidates, to perform preclinical research to identify new product candidates and to provide general and administrative support for these operations. We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations primarily through the sale of common stock in public offerings, private placements of preferred stock and warrants and through collaborations.

We have never been profitable and have incurred net losses in each year since inception. Our net loss was $48.7 million for the year ended December 31, 2014 and our accumulated deficit was $147.4 million as of December 31, 2014. Substantially all our net losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We expect our expenses will increase substantially in connection with our ongoing and planned activities, as we:

- conduct clinical studies for our Lenti-D and LentiGlobin product candidates
- increase research and development-related activities for the discovery and development of oncology product candidates in connection with our strategic collaboration with Celgene;
- continue our research and development efforts;
- manufacture clinical study materials and develop large-scale manufacturing capabilities;
- seek regulatory approval for our product candidates;
- add personnel to support our product development and commercialization efforts; and
- operate as a public company.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates, which we expect will take a number of years

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

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

Financial operations overview

Revenue

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

Collaboration revenue is generated exclusively from our collaboration arrangement with Celgene. The terms of this arrangement contain multiple deliverables, which include at inception: (i) discovery, research and development services, (ii) participation on the joint steering committee and (iii) participation on the patent committee. We recognize arrangement consideration allocated to each unit of accounting when all of the revenue recognition criteria in Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 605, Revenue Recognition, or ASC 605, are satisfied for that particular unit of accounting. Revenue from the Celgene arrangement associated with discovery, research and development services, joint steering committee services and patent committee services is recognized ratably over the associated period of performance, which is initially three years.

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

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

Research and development expenses

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

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

Research and development costs are expensed as incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites. We cannot determine with certainty the duration and completion costs of the current or future clinical studies of our product candidates or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs, and timing of clinical studies and development of our product candidates will depend on a variety of factors, including:

- the scope, rate of progress, and expense of our ongoing as well as any additional clinical studies and other research and development activities we undertake;
- future clinical study results;
- uncertainties in clinical study enrollment rates;
- changing standards for regulatory approval; and

· the timing and receipt of any regulatory approvals.

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

From inception through December 31, 2014, we have incurred $158.1 million in research and development expenses. We plan to increase our research and development expenses for the foreseeable future as we continue to advance the development of our Lenti-D and LentiGlobin product candidates, conduct research and development activities under our strategic collaboration with Celgene and continue the research and development of product candidates using the acquired Pregenen gene editing technology platform. Our research and development activities include the following:

· We are conducting a Phase II/III clinical study to examine the safety and efficacy of our Lenti-D product candidate in the treatment of CCALD. In October 2013, we announced that the first subject had been treated in this study.
· We are conducting a Phase I/II clinical study in the United States, Australia and Thailand to study the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with ß-thalassemia major. In March 2014, we announced that the first subject had been treated in this study.
· We are conducting a Phase I/II clinical study in France to study the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with ß-thalassemia major and severe SCD. In December 2013, we announced that the first subject ß-thalassemia major had been treated in this study and in October 2014, we announced that the first subject with SCD had been treated in this study.
· We have initiated a Phase I clinical study in the United States to study the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with severe SCD.
· We will continue to manufacture clinical study materials in support of our clinical studies.

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

	Year ended December 31,		
	2014	2013	2012
	(in thousands)		
Lenti-D	$12,137	$4,396	$3,966
LentiGlobin	21,444	8,490	5,259
Pre-clinical programs	6,651	783	—
Total direct research and development expense	40,232	13,669	9,225
Employee- and contractor-related expenses	6,771	9,152	5,742
Stock-based compensation expense	5,151	3,809	408
Platform-related expenses	5,112	1,067	727
Facility expenses	5,292	2,288	709
Other expenses	16	1,017	399
Unallocated personnel and other expenses	22,342	17,333	7,985
Total research and development expense	$62,574	$31,002	$17,210

General and administrative expenses

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

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research and development and potential commercialization of our product candidates. We also anticipate increased expenses related to audit, legal, regulatory, and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, director and officer insurance premiums, and investor relations costs associated with being a public company. Additionally, if and when we believe a regulatory approval of the first product candidate appears likely, we anticipate an increase in payroll and related expenses as a result of our preparation for commercial operations, especially as it relates to the sales and marketing of our product candidates.

Other income (expense), net

Other income and expense consists primarily of interest income earned on investments, the gain or loss associated with the change in the fair value of preferred stock warrants, foreign currency gain or loss and tax incentives from the Massachusetts Life Sciences Center.

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

Critical accounting policies and significant judgments and estimates

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

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

Revenue recognition

We have primarily generated revenue through collaboration arrangements, research arrangements and license arrangements with strategic partners and nonprofit organizations for the development and commercialization of product candidates. Additionally, we have generated revenue from research and development grant programs.

We recognize revenue in accordance with ASC 605. Accordingly, revenue is recognized for each unit of accounting when all of the following criteria are met:

·Persuasive evidence of an arrangement exists
·Delivery has occurred or services have been rendered
·The seller's price to the buyer is fixed or determinable

·Collectability is reasonably assured

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

Collaboration revenue

As of December 31, 2014, our collaboration revenue was generated exclusively from our collaboration arrangement with Celgene. The terms of this arrangement contains multiple deliverables, which include at inception: (i) discovery, research and development services, (ii) participation on the joint steering committee and (iii) participation on the patent committee. The collaboration arrangement also provides Celgene with the option to obtain a license to any product candidates resulting from the collaboration. Moreover, Celgene has the option to extend the term of the collaboration arrangement, first for a period of two years and then for an additional period of one year. Additionally, we have the sole right to manufacture or have manufactured supplies of vectors and associated payloads manufactured for incorporation into the associated product candidate in the event a product candidate is licensed. Non-refundable payments to us under this arrangement may include: (i) up-front research fees, (ii) product candidate license fees, (iii) extension term research fees, (iv) payments for the manufacture and supply of vectors and payloads, (v) payments based on the achievement of certain milestones and (vi) royalties on product sales. Additionally, we may elect to share in the costs incurred from the development, commercialization and manufacture of product candidates licensed by our collaborators and earn our share of the net profits or bear our share of the net losses generated from the sale of product candidates licensed by our collaborators.

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

Arrangement consideration that is fixed or determinable is allocated among the separate units of accounting using the relative selling price method. Then, the applicable revenue recognition criteria in ASC 605 are applied to each of the separate units of accounting in determining the appropriate period and pattern of recognition. We determine the selling price of a unit of accounting following the hierarchy of evidence prescribed by ASC 605-25. Accordingly, we determine the estimated selling price for units of accounting within each arrangement using vendor-specific objective evidence, or VSOE, of selling price, if available, third-party evidence, or TPE, of selling price if VSOE is not available, or best estimate of selling price, or BESP, if neither VSOE nor TPE is available. We typically use BESP to estimate the selling price, since we generally do not have VSOE or TPE of selling price for our units of accounting. Determining the BESP for a unit of accounting requires significant judgment. In developing the BESP for a unit of accounting, we consider applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. We validate the BESP for units of accounting by evaluating whether changes in the key assumptions used to determine the BESP will have a significant effect on the allocation of arrangement consideration between multiple units of accounting.

Options are considered substantive if, at the inception of the arrangement, we are at risk as to whether the collaboration partner will choose to exercise the option. Factors that we consider in evaluating whether an option is substantive include the overall objective of the arrangement, the benefit the collaborator might obtain from the arrangement without exercising the option, the cost to exercise the option and the likelihood that the option will be

exercised. For arrangements under which an option is considered substantive, we do not consider the item underlying the option to be a deliverable at the inception of the arrangement and the associated option fees are not included in allocable arrangement consideration, assuming the option is not priced at a significant and incremental discount. Conversely, for arrangements under which an option is not considered substantive or if an option is priced at a significant and incremental discount, we would consider the item underlying the option to be a deliverable at the inception of the arrangement and a corresponding amount would be included in allocable arrangement consideration. All of the options included in our collaboration arrangement have been determined to be substantive, and none of the options are priced at a significant and incremental discount.

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

We recognize revenue from the Celgene arrangement associated with discovery, research and development services, joint steering committee services and patent committee services ratably over the associated period of performance. If there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, then we recognize revenue under the arrangement on a straight-line basis over the period we are expect to complete our performance obligations. Conversely, if the pattern of performance in which the service is provided to the customer can be determined and objectively measurable performance measures exist, then we recognize revenue under the arrangement using the proportional performance method. Revenue recognized is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method or proportional performance method, as applicable, as of the period ending date.

At the inception of an arrangement that includes milestone payments, we evaluate whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether: (i) the consideration is commensurate with either our performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from our performance to achieve the milestone, (ii) the consideration relates solely to past performance and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. We evaluate factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the respective milestone and the level of effort and investment required to achieve the respective milestone in making this assessment. There is considerable judgment involved in determining whether a milestone satisfies all of the criteria required to conclude that a milestone is substantive. We have concluded that all of the clinical and regulatory milestones pursuant to its collaboration arrangement are substantive. Accordingly, in accordance with FASB ASC Topic 605-28, Revenue Recognition-Milestone Method, revenue from clinical and regulatory milestone payments will be recognized in its entirety upon successful accomplishment of the milestone, assuming all other revenue recognition criteria are met. Milestones that are not considered substantive would be recognized as revenue over the remaining period of performance, assuming all other revenue recognition criteria are met. Revenue from commercial milestone payments will be accounted for as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.

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

Business combinations

On June 30, 2014, we completed our acquisition of Pregenen for total consideration of $31.0 million, consisting of cash consideration of $5.1 million, common stock consideration of $19.3 million and contingent consideration with an estimated fair value of $6.6 million. The estimated fair value of the contingent consideration is based upon significant assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones are achieved and discount rates. The estimated fair value could materially differ from actual values or fair values determined using different assumptions.

This transaction was accounted for as a business combination under the acquisition method of accounting. Accordingly, the tangible assets and identifiable intangible assets acquired and liabilities assumed were recorded at fair value as of the date of acquisition, with the remaining purchase price recorded as goodwill. The estimated fair values of acquired assets and assumed liabilities were determined using the methods discussed in the following paragraphs and require significant judgment and estimates, which could materially differ from actual values and fair values determined using different methods or assumptions.

Goodwill

Goodwill represents the excess of the purchase price over the fair value of the net assets acquired when accounted for using the acquisition method of accounting for business combinations. Goodwill is not amortized but is evaluated for impairment within our single reporting unit on an annual basis, during the fourth quarter, or more frequently if an event occurs or circumstances change that would more-likely-than-not reduce the fair value of the reporting unit below its carrying amount. We have not recognized any impairment charges related to goodwill.

Intangible assets

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

Contingent consideration

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

Accrued research and development expenses

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

·CROs in connection with clinical studies;
·investigative sites in connection with clinical studies;
·vendors in connection with preclinical development activities; and
·vendors related to product manufacturing, development and distribution of clinical supplies.

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

Stock-based compensation

Stock-based awards

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

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

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

We estimate the fair value of our stock-based awards to employees and non-employees using the Black-Scholes option pricing model, which requires the input of highly subjective assumptions, including (i) the expected volatility of our stock, (ii) the expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Due to the lack of a public market for the trading of our common stock and a lack of company specific historical and implied volatility data, we based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. For these analyses, we select companies with comparable characteristics to ours including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We estimate the expected life of our employee stock options using the "simplified" method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option were based on the U.S. Treasury yield curve in effect during the period the options were granted.

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

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

	Year ended December 31,		
	2014	2013	2012
Expected volatility	82.3%	82.0%	79.6%
Expected term (in years)	6.0	6.1	6.1
Risk-free interest rate	1.8%	1.1%	1.0%
Expected dividend yield	0.0%	0.0%	0.0%
Weighted average exercise price per share	$26.92	$8.59	$2.20

Stock-based compensation totaled approximately $10.8 million for the year ended December 31, 2014 and $6.5 million for the year ended December 31, 2013. As of December 31, 2014, we had $22.1 million of total unrecognized compensation expense related to unvested stock options, net of related forfeiture estimates, which is expected to be recognized over a weighted-average remaining vesting period of approximately 2.9 years and $3.9 million of total unrecognized compensation expenses related to unvested restricted stock units, net of related forfeiture estimates, which is expected to be recognized over a weighted-average remaining vesting period of 1.5 years. We expect the impact of our stock-based compensation expense for stock options and restricted stock units granted to employees and non-employees to grow in future periods due to the current year and potential future increases in the value of our common stock and headcount.

Recently adopted accounting pronouncements

In May 2014, the FASB issued ASU No. 2014-09, Revenue from Contracts with Customers (Topic 606), which supersedes all existing revenue recognition requirements, including most industry-specific guidance. The new standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. The new standard will be effective for us on January 1, 2017. We are currently evaluating the method of adoption and the potential impact that Topic 606 may have on our financial position and results of operations.

In August 2014, the FASB issued ASU No. 2014-15, Presentation of Financial Statements – Going Concern ("ASU No. 2014-15"). The new guidance addresses management's responsibility to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. Management's evaluation should be based on relevant conditions and events that are known and reasonably knowable at the date that the financial statements are issued. The standard will be effective for the first interim period within annual reporting periods beginning after December 15, 2016. Early adoption is permitted. We are currently evaluating the potential impact that ASU No. 2014-15 may have on our financial position and results of operations.

Results of Operations

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

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

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

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

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

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

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

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

Comparison of the years ended December 31, 2013 and 2012:

	Year ended December 31,		
	2013	2012	Change
	(in thousands)		
Revenue:			
Collaboration revenue	$19,792	$—	$19,792
Research and license fees	389	340	49
Total revenue	20,181	340	19,841
Operating expenses:			
Research and development	31,002	17,210	13,792
General and administrative	14,126	6,846	7,280
Total operating expenses	45,128	24,056	21,072
Loss from operations	(24,947)	(23,716)	1,231
Other income (expense), net	(374)	46	420
Net loss	$(25,321)	$(23,670)	$1,651

Revenue. Total revenue was $20.2 million for the year ended December 31, 2013, compared to $0.3 million for the year ended December 31, 2012. The increase of $19.8 million was primarily due to the Celgene collaboration. In the year ended December 31, 2013, we recorded $19.8 million of the up-front payment related to research and development services from the Celgene collaboration, which was entered into in March 2013 and is expected to be recognized on a straight-line basis through March 2016, and $0.4 million of research and license fees.

Research and development expenses. Research and development expenses were $31.0 million for the year ended December 31, 2013, compared to $17.2 million for the year ended December 31, 2012. The increase of $13.8 million was primarily due to the increase in headcount and clinical trial related expenses to support the advancement of our programs, including the new Celgene collaboration, and included the following increases in expenses:

- Direct research and development expenses:
- $0.7 million of materials production costs in preparation for and upon initiation of the Starbeam, Northstar and HGB-205 clinical studies.
- $2.1 million of clinical trial related costs related to initiation of clinical studies in 2013.
- $0.5 million of costs for clinical and regulatory consultants to support regulatory filing and other clinical start-up activities.
- $1.6 million of platform and direct project lab supplies related to increased headcount and scale up process development activities.
- Personnel and other expenses:
- $6.8 million of employee compensation and benefits to support increased development activities related to the three clinical studies initiated and in support of preclinical programs in 2013. The increased headcount resulted in an incremental $0.2 million of recruiting and $0.4 million of travel expense.
- $1.6 million in facility-related expenses to accommodate increased lab headcount.

- $0.3 million in accelerated depreciation due to the shortened expected useful life of assets relating to our former corporate headquarters.

General and administrative expenses. General and administrative expenses were $14.1 million for the year ended December 31, 2013, compared to $6.8 million for the year ended December 31, 2012. The increase of $7.3 million was primarily due to the following increases in expenses: $4.3 million of employee-related costs to support our overall growth; $1.0 million of contractors and consultants expenses and $0.7 million of professional fees to support the requirements of being a public company; $0.5 million in general office expenses as a result of increased headcount; and $0.3 million in accelerated depreciation due to the shortened expected useful life of assets relating to our former corporate headquarters.

Other income (expense), net. Other income (expense), net, was $(0.4) million for the year ended December 31, 2013, compared to $0.05 million for the year ended December 31, 2012. The decrease of $0.4 million was primarily due to the re-measurement of fair value of our convertible preferred stock warrants and foreign currency gain.

Liquidity and Capital Resources

As of December 31, 2014, we had cash, cash equivalents and marketable securities of approximately $492.0 million. We expect cash, cash equivalents and marketable securities to fund operations through 2017. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. As of December 31, 2014, our funds are held in U.S. government agency securities, federally insured certificates of deposit and money market mutual funds invested in U.S. Treasuries or U.S. government agency securities.

We have incurred losses and cumulative negative cash flows from operations since our inception in April 1992, and as of December 31, 2014, we had an accumulated deficit of $147.4 million. We anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through a combination of equity offerings, debt financings, other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements.

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

Sources of Liquidity

Cash Flows

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

	Year ended December 31,		
	2014	2013	2012
	(in thousands)		
Net cash provided by (used in):			
Operating activities	$(59,693)	$43,450	$(21,044)
Investing activities	(157,193)	(9,823)	2,599
Financing activities	358,452	105,641	59,852
Net increase in cash and cash equivalents	$141,566	$139,268	$41,407

Cash Flows from Operating Activities. The net cash used in operating activities was $59.7 million for the year ended December 31, 2014 and primarily consisted of a net loss of $48.7 million adjusted for non-cash items including a

noncash benefit on release of tax valuation allowance of $11.8 million, stock-based compensation of $10.8 million, depreciation and amortization of $4.2 and a net decrease in operating assets and liabilities of $14.7 million. The significant items in the decrease in operating assets and liabilities include a decrease in deferred revenue of $24.9 million due to amortization of the up-front payment related to the Celgene collaboration, a decrease in accounts payable of $2.2 million and a decrease in prepaid expenses and other assets of $0.3 million offset by an increase in accrued expenses and other liabilities of $10.0 million and an increase in deferred rent of $2.0 million.

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

The net cash used in operating activities was $21.0 million for the year ended December 31, 2012, and consisted primarily of a net loss of $23.7 million adjusted for non-cash items including stock-based compensation expense of $0.8 million and depreciation of

$0.3 million and a net increase in operating assets and liabilities of $1.5 million. The significant items in the change in operating assets and liabilities include an increase in accounts payable of $0.4 million and accrued expenses and other liabilities of $1.4 million and a decrease in prepaid expenses and current assets of $0.1 million, offset by a decrease in deferred revenue of $0.3 million.

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

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

Net cash provided by investing activities for the year ended December 31, 2012 was $2.6 million and consisted primarily of proceeds from the sale of marketable securities of $3.5 million slightly offset by purchases of property and equipment of $0.9 million.

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

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

Net cash provided by financing activities for the year ended December 31, 2012 was the result of the sale of 120.4 million shares of our Series D preferred stock for net proceeds of $59.8 million.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations at December 31, 2014.

	Total	2015	2016 through 2017	2018 through 2019	After 2019
	(in thousands)				
150 Second Street Lease	$28,152	$3,166	$6,619	$7,023	$11,344
Facility operating leases, excluding 150 Second Street Lease (1)	717	486	231	—	—
License costs (2)	3,086	851	1,400	835	—

Total	$31,955	$4,503	$8,250	$7,858	$11,344

(1) Excludes $0.2 million of sublease receipts for 2015 for our 840 Memorial Drive leased space.

(2) License costs include annual license maintenance fee payments. We have not included annual license maintenance fees or minimum royalty payments after December 31, 2019, as we cannot estimate if they will occur.

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

- In connection with the Pregenen acquisition, we agreed to make contingent cash payments to the former equityholders of Pregenen. In accordance with accounting for business combinations guidance, these contingent cash payments are recorded as contingent consideration liabilities on our consolidated balance sheets at fair value. The aggregate, undiscounted amount of contingent consideration potentially payable is $135.0 million.
- Under a license agreement with Inserm-Transfert pursuant to which we license certain patents for use in human adrenoleukodystrophy therapy, we will be required to make payments based upon development, regulatory and commercial milestones for any products covered by the in-licensed intellectual property. The maximum aggregate payments we may be

obligated to pay for each of these milestone categories per product is €0.3, €0.2 and €1.6 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits. The royalty is subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.

- Under a license agreement with Institut Pasteur pursuant to which we license certain patents for use in ex vivo gene therapy, we will be required to make payments per product covered by the in-licensed intellectual property upon the achievement of development and regulatory milestones, depending on the indication and the method of treatment. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €1.5 and €2.0 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which varies slightly depending on the indication of the product. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the low single digits to mid-double digits depending on the nature of the sublicense. Starting in 2016, we will be required to make an annual maintenance payment, which is creditable against royalty payments on a year-by-year basis.
- Under a license agreement with the Board of Trustees of the Leland Stanford Junior University, or Stanford, pursuant to which we license the HEK293T cell line for use in gene therapy products, we are required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits that varies with net sales. The royalty is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage that is less than one percent. We are required to pay Stanford an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.
- Under a license agreement with the Massachusetts Institute of Technology, or MIT, pursuant to which we license various patents, we will be required to make a payment of $0.1 million based upon a regulatory filing milestone. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property by us or our sublicensees. The royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one percent. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the mid-single digits to low double digits. We are required to pay MIT an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.
- Under a license agreement with Research Development Foundation pursuant to which we license patents that involve lentiviral vectors, we will be required to make payments of $1.0 million based upon a regulatory milestone for each product covered by the in-licensed intellectual property. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which is reduced by half if during the ten year following first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.

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

On June 3, 2013, we entered into a nine-year building lease for approximately 43,600 square feet of space in Cambridge, Massachusetts, commencing on the earlier of the substantial completion of our build-out work or January 1, 2014. This lease was amended in June 2014 to add an additional approximately 9,900 square feet. The lease has monthly lease payments of $0.2 million for the first 12 months, which increased to $0.3 million per month beginning in December 2014 due to the lease amendment, with annual rent escalations thereafter and provides a rent abatement of $0.2 million per month for the first six months. The total operating lease obligation of the noncancellable term of this agreement is $29.5 million. In addition, the lease provides a contribution from the landlord towards the initial build-out of the space of up to $7.8 million. We have the option to extend this lease by an additional five years. In accordance with the lease, we entered into a cash-collateralized irrevocable standby letter of credit in the amount of $1.3 million, naming the landlord as beneficiary. This letter of credit was reduced to $1.0 million during the third quarter of 2014 and may be further reduced to $0.8 million and $0.6 million upon the first and second anniversaries of the rent commencement date, respectively. The building lease for our former corporate headquarters in Cambridge,

Massachusetts, expires on March 31, 2015. We relocated to the new space in December 2013 and ceased use of the facility during the first quarter of 2014.

We also lease approximately 3,900 square feet of office and laboratory space in Seattle, Washington, which lease expires in December 2016.

Off-Balance Sheet Arrangements

As of December 31, 2014, we did not have any off-balance sheet arrangements as defined in the rules and regulations of the SEC.

Item 7A. Quantitative and Qualitative Disclosures about Market Risks

We are exposed to market risk related to changes in interest rates. As of December 31, 2014 and 2013, we had cash, cash equivalents and marketable securities of $492.0 million and $206.3 million, respectively, primarily invested in U.S. Government agency securities, federally insured certificates of deposit and money market mutual funds invested in U.S. Treasuries or U.S. government agency securities. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase. If market interest rates were to increase immediately and uniformly by 100 basis points, or one percentage point, from levels at December 31, 2014, the net fair value of our interest-sensitive marketable securities would have resulted in a hypothetical decline of $0.9 million.

Item 8. Financial Statements and Supplementary Data

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

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

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

Management’s Annual Report on Internal Control Over Financial Reporting

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

• Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;

• Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and

• Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.Under the supervision and with the participation of management, including our principal executive and financial officers, we assessed our internal control over financial reporting as of December 31, 2014, based on criteria for effective internal control over financial reporting established in Internal Control — Integrated Framework (2013), issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Our management's assessment of the effectiveness of our internal control over financial reporting included testing and evaluating the design and operating effectiveness of our internal controls. In our management's opinion, we have maintained effective internal control over financial reporting as of December 31, 2014, based on criteria established in the COSO 2013 framework.

The effectiveness of the our internal control over financial reporting as of December 31, 2014 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which is included herein.

Inherent Limitations of Internal Controls

Our management, including our Chief Executive Officer and Chief Financial Officer, does not expect that our disclosure controls and procedures or our internal controls will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of the

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

Changes in Internal Control over Financial Reporting

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

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of

bluebird bio, Inc.

We have audited bluebird bio, Inc.’s internal control over financial reporting as of December 31, 2014, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). bluebird bio, Inc.’s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management’s Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the company’s internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

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

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

In our opinion, bluebird bio, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2014, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of bluebird bio, Inc. as of December 31, 2014 and 2013, and the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2014 of bluebird bio, Inc. and our report dated February 25, 2015 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 25, 2015

Item 9B. Other Information

Our policy governing transactions in our securities by our directors, officers, and employees permits our officers, directors and certain other persons to enter into trading plans complying with Rule 10b5-1 under the Securities Exchange Act of 1934, as amended. We have been advised that certain of our officers (including Jeffrey Walsh, Chief Operating Officer, Mitchell Finer, Chief Scientific Officer, David Davidson, Chief Medical Officer, Jason Cole, Senior Vice President and General Counsel and Eric Sullivan, Senior Director, Finance and Principal Accounting Officer) have entered into trading plans covering periods after the date of this annual report on Form 10-K in accordance with Rule 10b5-1 and our policy governing transactions in our securities. Generally, under these trading plans, the individual relinquishes control over the transactions once the trading plan is put into place. Accordingly, sales under these plans may occur at any time, including possibly before, simultaneously with, or immediately after significant events involving our company. We do not undertake to report Rule 10b5-1 trading plans that may be adopted by any officers or directors in the future, or to report any modifications or termination of any publicly announced trading plan, except to the extent required by law.

PART III

Item 10. Directors, Executive Officers, and Corporate Governance

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 11. Executive Compensation

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

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

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 13. Certain Relationships and Related Transactions and Director Independence

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 14. Principal Accountant Fees and Services

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

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PART IV

Item 15. Exhibits, Financial Statements and Schedules

(a)(1) Financial Statements.

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

(a)(2) Financial Statement Schedules.

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

(a)(3) Exhibits.

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

bluebird bio, Inc.

Index to consolidated financial statements

Report of independent registered public accounting firm

The Board of Directors and Stockholders of

bluebird bio, Inc.

We have audited the accompanying consolidated balance sheets of bluebird bio, Inc. as of December 31, 2014 and 2013, and the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2014. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of bluebird bio, Inc. at December 31, 2014 and 2013, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2014, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), bluebird bio, Inc.'s internal control over financial reporting as of December 31, 2014, based on the criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 25, 2015 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 25, 2015

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bluebird bio, Inc.

Consolidated Balance Sheets

(in thousands, except per share data)

	December 31,	
	2014	2013
Assets		
Current assets:		
Cash and cash equivalents	$347,845	$206,279
Marketable securities	125,710	—
Deferred tax assets	1,913	693
Prepaid expenses and other current assets	4,521	5,015
Total current assets	479,989	211,987
Marketable securities	18,448	—
Property and equipment, net	15,740	10,920
Intangible assets, net	28,219	—
Goodwill	13,128	—
Restricted cash and other non-current assets	1,215	1,483
Total assets	$556,739	$224,390
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$2,954	$4,359
Accrued expenses and other current liabilities	14,649	5,175
Deferred revenue, current portion	25,375	25,340
Total current liabilities	42,978	34,874
Deferred rent, net of current portion	8,674	6,740
Deferred revenue, net of current portion	5,302	30,208
Contingent consideration, net of current portion	6,321	—
Deferred tax liabilities	1,913	693
Other non-current liabilities	294	208
Total liabilities	65,482	72,723
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Preferred stock, $0.01 par value, 5,000 shares authorized; 0 shares issued and outstanding at December 31, 2014 and December 31, 2013	—	—
Common stock, $0.01 par value, 125,000 shares authorized; 32,340 and 23,940 shares issued and outstanding at December 31, 2014 and December 31, 2013, respectively	323	239
Additional paid-in capital	638,389	250,103
Accumulated other comprehensive loss	(71)	—
Accumulated deficit	(147,384)	(98,675)
Total stockholders' equity	491,257	151,667

Total liabilities and stockholders' equity	$556,739	$224,390

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except per share data)

	Year ended December 31,		
	2014	2013	2012
Revenue:			
Collaboration revenue	$25,031	$19,792	$—
Research and license fees	390	389	340
Total revenue	25,421	20,181	340
Operating expenses:			
Research and development	62,574	31,002	17,210
General and administrative	23,227	14,126	6,846
Change in fair value of contingent consideration	246	—	—
Total operating expenses	86,047	45,128	24,056
Loss from operations	(60,626)	(24,947)	(23,716)
Other income (expense), net:			
Interest income	152	29	5
Foreign currency gains (losses)	(163)	37	13
Re-measurement of warrants	—	(440)	28
Other income	131	—	—
Total other income (expense), net	120	(374)	46
Loss before income taxes	(60,506)	(25,321)	(23,670)
Benefit from income taxes	11,797	—	—
Net loss	$(48,709)	$(25,321)	$(23,670)
Other comprehensive loss:			
Unrealized loss on available-for-sale securities, net of tax	(71)	—	(1)
Total other comprehensive loss	(71)	—	(1)
Comprehensive loss	$(48,780)	$(25,321)	$(23,671)
Reconciliation of net loss to net loss applicable to common stockholders:			
Net loss	$(48,709)	$(25,321)	$(23,670)
Accretion and dividends on convertible preferred stock	—	—	(3,057)
Gain on extinguishment of convertible preferred stock	—	—	23,114
Net loss applicable to common stockholders	$(48,709)	$(25,321)	$(3,613)
Net loss per share applicable to common stockholders - basic and diluted:	$(1.83)	$(2.02)	$(13.79)
Weighted-average number of common shares used in computing net loss per share - basic and diluted:	26,546	12,555	262

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

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

(in thousands)

	Series A-1 convertible preferred stock		Series A-2 convertible preferred stock		Series B convertible preferred stock		Series C convertible preferred stock		Series D convertible preferred stock	
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount
Balance at December 31, 2011	12,981	$9,217	22,304	$15,837	115,204	$41,495	39,943	$15,854	-	$-
Issuance of Series D Preferred Stock, net of issuance costs	-	-	-	-	-	-	-	-	120,409	59,831
Accretion and dividends on convertible preferred stock	-	194	-	332	-	1,689	-	673	-	169
Gain on extinguishment of convertible preferred stock	-	(7,074)	-	(9,032)	-	(2,863)	-	(4,145)	-	-
Reclassification of Series A-1 Preferred Stock	(12,981)	(2,337)	-	-	-	-	-	-	-	-
Reclassification of Series A-1 Preferred Stock warrants	-	-	-	-	-	-	-	-	-	-
Vesting of restricted stock issued in exchange for nonrecourse note	-	-	-	-	-	-	-	-	-	-
Vesting of restricted stock	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-

Exercise of stock options										
Realized gain on marketable securities	-	-	-	-	-	-	-	-	-	-
Stock-based compensation	-	-	-	-	-	-	-	-	-	-
Net loss	-	-	-	-	-	-	-	-	-	-
Balance at December 31, 2012	-	$-	22,304	$7,137	115,204	$40,321	39,943	$12,382	120,409	$60,000

	Series A-1 convertible preferred stock		Common stock		Additional paid-in	Accumulated other comprehensive income	Accumulated	Total stockholders' equity
	Shares	Amount	Shares	Amount	capital	(loss)	deficit	(deficit)
Balance at December 31, 2011	-	$-	205	$ 2	7,732	$ 1	$ (63,442)	$ (55,707)
Issuance of Series D Preferred Stock, net of issuance costs	-	-	-	-	-	-	-	-
Accretion and dividends on convertible preferred stock	-	-	-	-	(3,057)	-	-	(3,057)
Gain on extinguishment of convertible preferred stock	-	-	-	-	9,356	-	13,758	23,114
Reclassification of Series A-1 Preferred Stock	12,981	2,337	-	-	-	-	-	2,337
Reclassification of Series A-1 Preferred Stock warrants	-	-	-	-	394	-	-	394
Vesting of restricted stock issued in exchange for nonrecourse note	-	-	82	1	(1)	-	-	-
Vesting of restricted stock	-	-	12	-	-	-	-	-
Exercise of stock options	-	-	10	-	21	-	-	21
Realized gain on marketable securities	-	-	-	-	-	(1)	-	(1)
Stock-based compensation	-	-	-	-	822	-	-	822
Net loss	-	-	-	-	-	-	(23,670)	(23,670)
Balance at December 31, 2012	12,981	$2,337	309	$ 3	$ 15,267	$ -	$ (73,354)	$ (55,747)

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bluebird bio, Inc.

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

(in thousands)

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

Stock-based compensation										
Net loss	-	-	-	-	-	-	-	-	-	-
Balance at December 31, 2013	-	$ -	-	$ -	-	$ -	-	$ -	-	$ -

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

bluebird bio, Inc.

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

(in thousands)

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

	Series A-1 convertible preferred stock		Common stock		Additional paid-in	Accumulated other comprehensive income	Accumulated	Total stockholders' equity
	Shares	Amount	Shares	Amount	capital	(loss)	deficit	(deficit)
Balance at December 31, 2013	-	$ -	23,940	$ 239	$ 250,103	$ -	$ (98,675)	$ 151,667
Vesting of restricted stock issued in exchange for nonrecourse note	-	-	69	1	(1)	-	-	-
Issuance of common stock upon public offering,	-	-	6,498	65	352,977	-	-	353,042

net of issuance costs of $23,295								
Issuance of common stock in connection with acquisition	-	-	411	4	19,470	-	-	19,474
Exercise of common stock warrants	-	-	114	1	(1)	-	-	-
Exercise of stock options	-	-	1,306	13	5,036	-	-	5,049
Issuance of common stock in exchange for consulting services to non-employees	-	-	2	-	42	-	-	42
Stock-based compensation	-	-	-	-	10,763	-	-	10,763
Unrealized loss on available-for-sale securities, net of tax	-	-	-	-	-	(71)	-	(71)
Net loss	-	-	-	-	-	-	(48,709)	(48,709)
Balance at December 31, 2014	-	$ -	32,340	$ 323	$ 638,389	$ (71)	$ (147,384)	$ 491,257

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Consolidated Statements of Cash Flows

(in thousands)

	Year ended December 31,		
	2014	2013	2012
Operating activities			
Net loss	$(48,709)	$(25,321)	$(23,670)
Adjustments to reconcile net loss to net cash (used in) provided by operating activities:			
Noncash benefit on release of income tax valuation allowance	(11,797)	—	—
Depreciation and amortization	4,228	941	301
Stock-based compensation expense	10,763	6,491	822
Remeasurement of contingent consideration	246	—	—
Issuance of restricted common stock in exchange for consulting services to non-employees	168	—	—
Re-measurement of warrants	—	440	(28)
Loss on disposal of equipment	3	9	10
Other non-cash items	139	—	—
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	307	(4,214)	93
Accounts payable	(2,249)	2,067	380
Accrued expenses and other liabilities	9,969	761	1,336
Deferred revenue	(24,871)	54,868	(340)
Deferred rent	2,110	7,408	52
Net cash (used in) provided by operating activities	(59,693)	43,450	(21,044)
Investing activities			
Restricted cash	209	(1,153)	(40)
Purchase of property and equipment	(8,708)	(8,670)	(867)
Purchases of marketable securities	(174,981)	—	—
Proceeds from sales or maturities of marketable securities	30,960	—	3,506
Acquisition of business, net of cash acquired	(4,673)	—	—
Net cash (used in) provided by investing activities	(157,193)	(9,823)	2,599
Financing activities			
Proceeds from public offering of common stock, net of issuance costs	353,226	104,921	—
Proceeds from issuance of convertible preferred stock, net of issuance costs	—	—	59,831
Repayment of nonrecourse note collateralized by restricted stock	—	344	—
Proceeds from exercise of stock options and issuance of common stock	5,226	376	21
Net cash provided by financing activities	358,452	105,641	59,852
Increase in cash and cash equivalents	141,566	139,268	41,407
Cash and cash equivalents at beginning of period	206,279	67,011	25,604
Cash and cash equivalents at end of period	$347,845	$206,279	$67,011
Non-cash investing and financing activities:			

Purchases of property and equipment included in accounts payable and accrued expenses	$387	$1,924	$—
Offering expenses included in accounts payable and accrued expenses	$183	$—	$—
Accretion and dividends on convertible preferred stock	$—	$—	$3,057
Gain on extinguishment of convertible preferred stock	$—	$—	$23,114
Reclassification of warrants to additional paid-in capital	$—	$655	$394
Reclassification of Series A-1 Preferred Stock to common stock	$—	$-	$2,337
Conversion of preferred stock to common stock upon closing of IPO	$—	$122,178	$—
Stock option exercise proceeds receivable	$98	$107	$—

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Notes to Consolidated Financial Statements

1. Description of the business

bluebird bio, Inc. (the "Company" or "bluebird") was incorporated in Delaware on April 16, 1992, and is headquartered in Cambridge, Massachusetts. The Company was formed to develop, manufacture and market therapies to safely and effectively deliver genes useful in the treatment of serious human diseases. Since its inception, the Company has devoted substantially all of its resources to its research and development efforts relating to its product candidates, including activities to manufacture product candidates, conduct clinical studies of its product candidates, perform preclinical research to identify new product candidates and provide general and administrative support for these operations.

On June 30, 2014, the Company acquired all of the outstanding capital stock of Precision Genome Engineering, Inc. ("Pregenen") and in connection therewith, obtained the rights to Pregenen's gene editing and cell signaling technology. See Note 12, "Business combinations," for additional information.

In July 2014, the Company sold 3,450,000 shares of common stock (inclusive of 450,000 shares of common stock sold by the Company pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $34.00 per share. The aggregate net proceeds received by the Company from the offering were $109.8 million, net of underwriting discounts and commissions and offering expenses payable by the Company of approximately $7.5 million.

In December 2014, the Company sold 3,047,500 shares of common stock (inclusive of 397,500 shares of common stock sold by the Company pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $85.00 per share. The aggregate net proceeds received by the Company from the offering were $243.3 million, net of underwriting discounts and commissions and estimated offering expenses payable by the Company of approximately $15.8 million.

As of December 31, 2014, the Company had cash, cash equivalents and marketable securities of $492.0 million. Although the Company has incurred recurring losses, the Company expects its cash, cash equivalents and marketable securities will be sufficient to fund current operations for at least the next twelve months.

2. Summary of significant accounting policies and basis of presentation

Basis of presentation and principles of consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries: Precision Genome Engineering, Inc., bluebird bio France – SARL, bluebird bio Australia Pty Ltd. and bluebird bio Securities Corporation. All intercompany balances and transactions have been eliminated in consolidation. The assets acquired and liabilities assumed in connection with the Company's acquisition of Pregenen were recorded at their fair values as of June 30, 2014, the date of the acquisition, and the operating results of Pregenen

have been consolidated with those of the Company from the date of acquisition. These consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

Foreign currency translation

The Company's consolidated financial statements are prepared in U.S. dollars. Its foreign subsidiary uses the U.S. dollar as its functional currency and maintains its records in the local currency. Nonmonetary assets and liabilities are re-measured at historical rates and monetary assets and liabilities are re-measured at exchange rates in effect at the end of the reporting period. Income statement accounts are re-measured at average exchange rates for the reporting period. The resulting gains or losses are included in foreign currency gains (losses) in the consolidated statements of operations and comprehensive loss.

Use of estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts in the financial statements and accompanying notes. Actual results could materially differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant

judgment in this process. In addition, other factors may affect estimates, including: expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements. Estimates are used in the following areas, among others: acquisition-date fair value and subsequent fair value estimates used to assess potential impairment of long-lived assets, including goodwill and intangible assets, contingent consideration, stock-based compensation expense, accrued expenses, revenue and income taxes.

Segment information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision making group, in making decisions on how to allocate resources and assess performance. The Company views its operations and manages its business in one operating segment. All material long-lived assets of the Company reside in the United States.

Cash and cash equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at acquisition to be cash equivalents. Cash and cash equivalents include cash held in banks and money market accounts. Cash equivalents are reported at fair value.

Marketable securities

The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Marketable securities with a remaining maturity date greater than one year are classified as non-current. Available-for-sale securities are maintained by an investment manager and may consist of U.S. Treasury securities, U.S. government agency securities, federally insured certificates of deposit and money market funds invested in U.S. Treasuries or U.S. government agency securities. Available-for-sale securities are carried at fair value with the unrealized gains and losses included in other comprehensive income as a component of stockholders' equity until realized. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense. Realized gains and losses are determined using the specific identification method and are included in other income (expense).

If any adjustment to fair value reflects a decline in value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is "other-than-temporary" and, if so, mark the investment to market through a charge to the Company's statement of operations and comprehensive loss.

Concentrations of credit risk and off-balance sheet risk

Financial instruments that subject the Company to credit risk primarily consist of cash and cash equivalents and available-for-sale securities. The Company maintains its cash and cash equivalent balances with high-quality financial institutions and, consequently, the Company believes that such funds are subject to minimal credit risk. The Company's available-for-sale investments primarily consist of U.S. government agency securities and federally insured certificates of deposit and potentially subject the Company to concentrations of credit risk. The Company has adopted an investment policy which limits the amounts the Company may invest in any one type of investment and requires all investments held by the Company to be at least AA+/Aa1 rated, thereby reducing credit risk exposure.

Fair value of financial instruments

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. FASB ASC Topic 820, Fair Value Measurements and Disclosures ("ASC 820"), establishes a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used when available. Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The three levels of the fair value hierarchy are described below:

Level 1—Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly.

Level 3—Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and unobservable.

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

Items measured at fair value on a recurring basis include a warrant liability (Note 8), marketable securities (Note 3) and contingent consideration (Note 12). The carrying amounts of accounts payable and accrued expenses approximate their fair values due to their short-term maturities.

Business combinations

On June 30, 2014, the Company completed its acquisition of Pregenen for total consideration of $31.0 million, consisting of cash consideration of $5.1 million, common stock consideration of $19.3 million and contingent consideration with an estimated fair value of $6.6 million on the date of purchase. The estimated fair value of the contingent consideration is based upon significant assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones are achieved and discount rates. The estimated fair value could materially differ from actual values or fair values determined using different assumptions. See Note 4, "Fair value measurements," for additional information.

This transaction was accounted for as a business combination under the acquisition method of accounting. Accordingly, the tangible assets and identifiable intangible assets acquired and liabilities assumed were recorded at fair value as of the date of acquisition, with the excess purchase price recorded as goodwill. The estimated fair values of the assets acquired and liabilities assumed at the date of acquisition are summarized in Note 12, "Business combinations." The estimated fair values of acquired assets and assumed liabilities were determined using the methods discussed in the following paragraphs and require significant judgment and estimates, which could materially differ from actual values and fair values determined using different methods or assumptions.

Goodwill

Goodwill represents the excess of the purchase price over the fair value of the net assets acquired when accounted for using the acquisition method of accounting for business combinations. Goodwill is not amortized but is evaluated for impairment within the Company's single reporting unit on an annual basis, during the fourth quarter, or more frequently if an event occurs or circumstances change that would more-likely-than-not reduce the fair value of the Company's reporting unit below its carrying amount. The Company has not recognized any impairment charges related to goodwill.

Intangible assets

Intangible assets consist of acquired core technology with finite lives. The Company amortizes its intangible assets using the straight-line method over their estimated economic lives. The Company evaluates the potential impairment of intangible assets if events or changes in circumstances indicate that the carrying amount of the assets may not be fully recoverable or that the useful lives of these assets are no longer appropriate. The impairment test is based on a

comparison of the undiscounted cash flows expected to be generated from the use of the asset group and its eventual disposition to the carrying value of the asset group. If impairment is indicated, the asset is written down by the amount by which the carrying value of the asset exceeds the related fair value of the asset. The Company has not recognized an impairment charge related to intangible assets.

Contingent consideration

Each reporting period, the Company revalues the contingent consideration obligations associated with business combinations to their fair value and records within operating expenses increases in their fair value as contingent consideration expense and decreases in the fair value as contingent consideration income. Changes in contingent consideration result from changes in the assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones are achieved and the discount rate used to estimate the fair value of the liability. Contingent consideration may change significantly as development of the Company's programs in certain indications progress and additional data are obtained, impacting the Company's assumptions. The assumptions used in estimating fair value require significant judgment. The use of different assumptions and judgments could result in a materially different estimate of fair value. See Note 4, "Fair value measurements," for additional information.

Property and equipment

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

Asset	Estimated useful life
Computer equipment and software	3 years
Office and laboratory equipment	2 -5 years
Leasehold improvements	Shorter of the useful life or remaining lease term

Impairment of long-lived assets

The Company reviews long-lived assets when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value, which is measured based on the projected discounted future net cash flows arising from the assets. No impairment losses have been recorded during the years ended December 31, 2014, 2013 and 2012.

Warrants to purchase convertible preferred stock

In conjunction with various financing transactions, the Company issued warrants to purchase shares of the Company's Series A-1 convertible preferred stock ("Series A-1 Preferred Stock") and Series B convertible preferred stock ("Series B Preferred Stock"). Prior to July 23, 2012, the Company's Series A-1 Preferred Stock and Series B Preferred Stock were subject to a redemption provision that was outside of the Company's control. Therefore, the associated shares were presented as temporary equity. Consequently, the warrants to purchase shares of Series A-1 Preferred Stock and Series B Preferred Stock were accounted for as liabilities through July 23, 2012 and adjusted to fair value at the end of each reporting period. The fair value of the warrants classified as liabilities is estimated using the Black-Scholes option pricing model. The estimates in the Black-Scholes option pricing model are based, in part, on subjective assumptions, including, stock price volatility, term of the warrants, risk free interest rate, dividend yield, and fair value of the preferred stock underlying the warrants. Such assumptions could differ materially in the future. The re-measurement gain or loss associated with the change in the fair value of the preferred stock warrant liability from the prior period is recognized as a component of other income (expense), net.

On July 23, 2012, in connection with the sale of the Company's Series D convertible preferred stock ("Series D Preferred Stock") and the associated modifications to the rights, preferences and privileges of the then-existing series of preferred stock, the Series A-1 Preferred Stock was reclassified to permanent equity because the redemption rights were relinquished and no liquidation preferences were obtained. Additionally, the fair value of the warrants to purchase shares of Series A-1 Preferred Stock as of July 23, 2012 were correspondingly reclassified to additional paid-in capital consistent with the treatment of the associated shares of preferred stock. All other classes of preferred stock remained classified within temporary equity as of December 31, 2012, due to their associated liquidation preferences. Due to these remaining liquidating preferences, the warrants to purchase shares of Series B Preferred Stock remained classified within liabilities as of December 31, 2012.

Upon closing of the IPO, all warrants exercisable for convertible preferred stock were automatically converted into warrants exercisable for common stock, resulting in the reclassification of the related convertible preferred stock warrant liability to additional paid-in capital.

Revenue recognition

The Company has primarily generated revenue through collaboration arrangements, research arrangements and license arrangements with strategic partners and nonprofit organizations for the development and commercialization of product candidates. Additionally, the Company has generated revenue from research and development grant programs.

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

Persuasive evidence of an arrangement exists
Delivery has occurred or services have been rendered
The seller’s price to the buyer is fixed or determinable
Collectability is reasonably assured
F-12

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

Collaboration revenue

As of December 31, 2014, the Company's collaboration revenue is generated exclusively from its collaboration arrangement with Celgene Corporation ("Celgene"). The terms of this arrangement contain multiple deliverables, which include at inception: (i) discovery, research and development services, (ii) participation on the joint steering committee and (iii) participation on the patent committee. The collaboration arrangement also provides Celgene with the option to obtain a license to any product candidates resulting from the collaboration. Moreover, Celgene has the option to extend the term of the collaboration arrangement, first for a period of two years and then for an additional period of one year. Additionally, the Company has the sole right to manufacture or have manufactured supplies of vectors and associated payloads manufactured for incorporation into the associated product candidate in the event a product candidate is licensed. Non-refundable payments to the Company under this arrangement may include: (i) up-front research fees, (ii) product candidate license fees, (iii) extension term research fees, (iv) payments for the manufacture and supply of vectors and payloads, (v) payments based on the achievement of certain milestones and (vi) royalties on product sales. Additionally, the Company may elect to share in the costs incurred from the development, commercialization and manufacture of product candidates licensed by its collaborators and earn its share of the net profits or bear its share of the net losses generated from the sale of product candidates licensed by its collaborators.

The Company analyzes multiple-element arrangements based on the guidance in FASB ASC Topic 605-25, Revenue Recognition-Multiple-Element Arrangements ("ASC 605-25"). Pursuant to the guidance in ASC 605-25, the Company evaluates multiple-element arrangements to determine (1) the deliverables included in the arrangement and (2) whether the individual deliverables represent separate units of accounting or whether they must be accounted for as a combined unit of accounting. This evaluation involves subjective determinations and requires management to make judgments about the individual deliverables and whether such deliverables are separable from the other aspects of the contractual relationship. Deliverables are considered separate units of accounting provided that: (i) the delivered item(s) has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially in the control of the Company. In assessing whether an item has standalone value, the Company considers factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the collaboration partner can use the other deliverable(s) for their intended purpose without the receipt of the remaining element(s), whether the value of the deliverable is dependent on the undelivered item(s) and whether there are other vendors that can provide the undelivered element(s). The Company's collaboration arrangement does not contain a general right of return relative to the delivered item(s).

Arrangement consideration that is fixed or determinable is allocated among the separate units of accounting using the relative selling price method. Then, the applicable revenue recognition criteria in ASC 605-25 are applied to each of the separate units of accounting in determining the appropriate period and pattern of recognition. The Company determines the selling price of a unit of accounting following the hierarchy of evidence prescribed by ASC 605-25. Accordingly, the Company determines the estimated selling price for units of accounting within each arrangement using vendor-specific objective evidence ("VSOE") of selling price, if available, third-party evidence ("TPE") of selling price if VSOE is not available, or best estimate of selling price ("BESP") if neither VSOE nor TPE is available. The Company typically uses BESP to estimate the selling price, since it generally does not have VSOE or TPE of selling price for its units of accounting. Determining the BESP for a unit of accounting requires significant judgment. In developing the BESP for a unit of accounting, the Company considers applicable market conditions and relevant

entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. The Company validates the BESP for units of accounting by evaluating whether changes in the key assumptions used to determine the BESP will have a significant effect on the allocation of arrangement consideration between multiple units of accounting.

Options are considered substantive if, at the inception of the arrangement, the Company is at risk as to whether the collaboration partner will choose to exercise the option. Factors that the Company considers in evaluating whether an option is substantive include the overall objective of the arrangement, the benefit the collaborator might obtain from the arrangement without exercising the option, the cost to exercise the option and the likelihood that the option will be exercised. For arrangements under which an option is considered substantive, the Company does not consider the item underlying the option to be a deliverable at the inception of the arrangement and the associated option fees are not included in allocable arrangement consideration, assuming the option is not priced at a significant and incremental discount. Conversely, for arrangements under which an option is not considered substantive or if an option is priced at a significant and incremental discount, the Company would consider the item underlying the option to be a deliverable at the inception of the arrangement and a corresponding amount would be included in allocable arrangement consideration. All of the options included in the Company’s collaboration arrangement have been determined to be substantive, and none of the options are priced at a significant and incremental discount.

The Company recognizes arrangement consideration allocated to each unit of accounting when all of the revenue recognition criteria in ASC 605-25 are satisfied for that particular unit of accounting. The Company will recognize as revenue arrangement consideration attributed to licenses that have standalone value from the other deliverables to be provided in an arrangement upon delivery. The Company will recognize as revenue arrangement consideration attributed to licenses that do not have standalone value from the other deliverables to be provided in an arrangement over the Company's estimated performance period as the arrangement would be accounted for as a single unit of accounting.

The Company recognizes revenue from the Celgene arrangement associated with discovery, research and development services, joint steering committee services and patent committee services ratably over the associated period of performance. If there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, then the Company recognizes revenue under the arrangement on a straight-line basis over the period the Company is expected to complete its performance obligations. Conversely, if the pattern of performance in which the service is provided to the customer can be determined and objectively measurable performance measures exist, then the Company recognizes revenue under the arrangement using the proportional performance method. Revenue recognized is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method or proportional performance method, as applicable, as of the period ending date.

At the inception of an arrangement that includes milestone payments, the Company evaluates whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether: (i) the consideration is commensurate with either the Company's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the Company's performance to achieve the milestone, (ii) the consideration relates solely to past performance and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. The Company evaluates factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the respective milestone and the level of effort and investment required to achieve the respective milestone in making this assessment. There is considerable judgment involved in determining whether a milestone satisfies all of the criteria required to conclude that a milestone is substantive. The Company has concluded that all of the clinical and regulatory milestones pursuant to its collaboration arrangement are substantive. Accordingly, in accordance with FASB ASC Topic 605-28, Revenue Recognition-Milestone Method, revenue from clinical and regulatory milestone payments will be recognized in its entirety upon successful accomplishment of the milestone, assuming all other revenue recognition criteria are met. Milestones that are not considered substantive would be recognized as revenue over the remaining period of performance, assuming all other revenue recognition criteria are met. Revenue from commercial milestone payments will be accounted for as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.

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

Research fees and license fees

The terms of the Company's research agreements and license agreements include delivery of an intellectual property license or the performance of research and development activities. The Company does not have any material research arrangements or license arrangements that contain multiple deliverables. The Company is compensated under research arrangements and license arrangements through nonrefundable up-front payments and future royalties on net product sales. Research fees are recognized as revenue on a straight-line basis over the period that the research services are expected to be performed unless the Company's pattern of performance can be determined to be other than straight-line, in which case, the Company uses the proportional performance method. Nonrefundable license fees are recognized as revenue upon delivery provided there are no undelivered elements in the arrangement.

Research and development expenses

Research and development costs are charged to expense as costs are incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, clinical study and related clinical manufacturing costs, contract services and other related costs. Research and development costs, including up-front fees and milestones paid to collaborators, are also expensed as incurred. In circumstances where amounts have been paid in excess of costs incurred, the Company records a prepaid expense.

Stock-based compensation

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

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

The Company expenses restricted stock unit awards to employees based on the fair value of the award on a straight-line basis over the associated service period of the award. Awards of restricted stock to non-employees are adjusted through share-based compensation expense at each reporting period end to reflect the current fair value of such awards and expensed using an accelerated attribution model.

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

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

Consistent with the guidance in FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees, the fair value of each non-employee stock option and warrant award is estimated at the date of grant using the Black-Scholes option pricing model with assumptions generally consistent with those used for employee stock options, with the exception of expected term, which is over the contractual life.

Other Income and Expense

In March 2014, the Company received an award of $0.3 million of tax incentives from the Massachusetts Life Sciences Center, which will allow the Company to monetize approximately $0.3 million of state research and

development tax credits. In exchange for these incentives, the Company pledged to hire an incremental fifteen employees and to maintain the additional headcount through at least December 31, 2018. Failure to do so could result in the Company being required to repay some or all of these incentives. As the Company met the additional headcount condition during the quarter ended June 30, 2014 and continues to meet such condition during the year ended December 31, 2014, the Company continues to defer and amortize the benefit of this monetization on a straight-line basis over the remaining five-year performance period in other income (expense).

Income taxes

Income taxes are recorded in accordance with FASB ASC Topic 740, Income Taxes (“ASC 740”), which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in

effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2014 and 2013, the Company does not have any significant uncertain tax positions.

Net loss per share

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

The Company follows the two-class method when computing net income (loss) per share in periods when issued shares that meet the definition of participating securities are outstanding. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to received dividends as if all income for the period had been distributed. Accordingly, in periods in which the Company reports a net loss attributable to common stockholders when participating securities are outstanding, losses are not allocated to the participating securities.

Comprehensive loss

Comprehensive loss is comprised of net loss and other comprehensive income or loss. Other comprehensive income or loss consists of unrealized gains and losses on marketable securities and foreign currency translation adjustments.

Subsequent events

The Company considers events or transactions that occur after the balance sheet date, but prior to the issuance of the financial statements to provide additional evidence relative to certain estimates or to identify matters that require additional disclosure.

Recently adopted accounting pronouncements

During the quarter ended June 30, 2014, the FASB issued ASU No. 2014-09, Revenue from Contracts with Customers (“ASU No. 2014-09”), which supersedes all existing revenue recognition requirements, including most industry-specific guidance. The new standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. The new standard will be effective on January 1, 2017 and early adoption is not permitted for public entities. The Company is currently evaluating the potential impact that ASU No. 2014-09 may have on its financial position and results of operations.

During the quarter ended September 30, 2014, the FASB issued ASU No. 2014-15, Presentation of Financial Statements – Going Concern (“ASU No. 2014-15”). The new guidance addresses management’s responsibility to evaluate

whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. Management's evaluation should be based on relevant conditions and events that are known and reasonably knowable at the date that the financial statements are issued. The standard will be effective for the first interim period within annual reporting periods beginning after December 15, 2016. Early adoption is permitted. The Company is currently evaluating the potential impact that ASU No. 2014-15 may have on its financial position and results of operations.

3. Marketable securities

The following table summarizes the available-for-sale securities held at December 31, 2014 (in thousands):

Description	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
December 31, 2014				
U.S. government agency securities	$131,589	$ 6	$ (59)	$131,536
Certificates of deposit	12,640	—	(18)	12,622
Total	$144,229	$ 6	$ (77)	$144,158

The Company did not hold any available-for-sale securities as of December 31, 2013. No available-for-sale securities held as of December 31, 2014 had remaining maturities greater than two years.

4. Fair value measurements

The following table sets forth the Company's assets and liabilities that are measured at fair value on a recurring basis as of December 31, 2014 and 2013 (in thousands):

Description	Total	Quoted prices in active markets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
December 31, 2014				
Assets:				
Cash and cash equivalents	$347,845	$347,845	$—	$ —
Marketable securities:				
U.S. government agency securities	131,536	—	131,536	—
Certificates of deposit	12,622	—	12,622	—
Total assets	$492,003	$347,845	$144,158	$ —
Liabilities:				
Contingent consideration	$6,796	$—	$—	$ 6,796
Total liabilities	$6,796	$—	$—	$ 6,796
December 31, 2013				
Total cash and cash equivalents	$206,279	$206,279	$—	$ —

Cash and cash equivalents

The Company considers all highly liquid securities with original final maturities of three months or less from the date of purchase to be cash equivalents. As of December 31, 2014 and 2013, cash and cash equivalents comprise funds in cash and money market accounts.

Marketable securities

The amortized cost of available-for-sale securities is adjusted for amortization of premiums and accretion of discounts to maturity. At December 31, 2014, the balance in the Company's accumulated other comprehensive loss was composed solely of activity related to the Company's available-for-sale marketable securities. There were no realized gains or losses recognized on the sale or maturity of available-for-sale securities during the years ended December 31, 2014 or 2013, and as a result, the Company did not reclassify any amount out of accumulated other comprehensive income for the same periods.

The aggregate fair value of securities held by the Company in an unrealized loss position for less than twelve months as of December 31, 2014 was $134.4 million, which consisted of 52 certificates of deposit and 7 U.S. government agency securities. The Company has the intent and ability to hold such securities until recovery. The Company determined that there was no material change in the credit risk of the above investments. As a result, the Company determined it did not hold any investments with an other-than-temporary impairment as of December 31, 2014.

Contingent consideration

In connection with the acquisition of Pregenen, the Company recorded contingent consideration pertaining to the amounts potentially payable to Pregenen's former equityholders pursuant to the Stock Purchase Agreement by and among the Company, Pregenen and Pregenen's former equityholders. Contingent consideration is measured at fair value and is based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The valuation of contingent consideration uses assumptions the Company believes would be made by a market participant. The Company assesses these estimates on an on-going basis as additional data impacting the assumptions is obtained. Future changes in the fair value of contingent consideration related to updated assumptions and estimates are recognized within the consolidated statements of operations and comprehensive loss.

Contingent consideration may change significantly as development progresses and additional data are obtained, impacting the Company's assumptions regarding probabilities of successful achievement of related milestones used to estimate the fair value of the liability and the timing in which they are expected to be achieved. In evaluating the fair value information, considerable judgment is required to interpret the market data used to develop the estimates. The estimates of fair value may not be indicative of the amounts that could be realized in a current market exchange. Accordingly, the use of different market assumptions and/or different valuation techniques could result in materially different fair value estimates.

The significant unobservable inputs used in the measurement of fair value of the Company's contingent consideration are probabilities of successful achievement of preclinical, clinical and commercial milestones, the period in which these milestones are expected to be achieved ranging from 2015 to 2026 and discount rates ranging from 10.8% to 14.8%. Significant increases or decreases in any of the probabilities of success would result in a significantly higher or lower fair value measurement, respectively. Significant increases or decreases in these other inputs would result in a significantly lower or higher fair value measurement, respectively.

The table below provides a roll-forward of fair value of the Company's contingent consideration obligations which include Level 3 inputs (in thousands):

	Year ended December 31, 2014
Beginning balance	$ —
Additions	6,550
Changes in fair value	246
Payments	—
Ending balance	$ 6,796

As of December 31, 2014, $0.5 million of the fair value of the Company's total contingent consideration obligations was reflected as components of accrued expenses and other current liabilities within the consolidated balance sheets, with the remaining balances of $6.3 million reflected as a non-current liability.

5. Property and equipment, net

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

	December 31,	
	2014	2013
Computer equipment and software	$814	$576
Office equipment	786	780
Laboratory equipment	7,223	3,758
Leasehold improvements	10,318	7,260
Total property and equipment	19,141	12,374
Less accumulated depreciation and amortization	(3,401)	(1,454)
Property and equipment, net	$15,740	$10,920

Depreciation and amortization expense related to property and equipment was $2.3 million, $0.9 million and $0.3 million for the years ending December 31, 2014, 2013, and 2012, respectively.

6. Restricted cash

As of December 31, 2014 and 2013, the Company maintained letters of credit of $1.2 million and $1.4 million, respectively, which are required to be collateralized with a bank account at a financial institution in accordance with the Company's current and former headquarters' lease agreements.

7. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities consist of the following (in thousands):

	December 31,	
	2014	2013
Employee compensation	$4,943	$1,740
Accrued goods and services	7,358	2,119
Accrued professional fees	428	305
Deferred rent, current portion	914	738
Contingent consideration, current portion	475	—
Other	531	273
Total accrued expenses and other current liabilities	$14,649	$5,175

8. Warrants

Warrants outstanding consist of the following (in thousands):

	As of December 31,	
	2014	2013
Warrants to purchase Common Stock	177	338
	177	338

As of December 31, 2012, the Company had outstanding warrants to purchase 6,512,650 shares of capital stock. Upon the closing of the Company's IPO on June 24, 2013, all of the warrants exercisable for convertible preferred stock were automatically converted into warrants exercisable for 337,952 shares of common stock, of which 307,648 and 30,304 were exercisable at $12.55 and $6.19 per share, respectively, and expire between November 16, 2015 and April 15, 2019. Each warrant is exercisable on either a physical settlement or net share settlement basis. During the years ended December 31, 2014 and 2013, there were 160,676 and 102,394 warrants exercised, respectively, and no cancellations or expirations.

In conjunction with the automatic conversion of all warrants exercisable for convertible preferred stock into warrants exercisable for common stock, the Company reclassified the related convertible preferred stock warrant liability to additional paid-in capital. The warrant liability was re-measured to fair value prior to reclassification to additional paid-in capital. As of December 31, 2014 and 2013, the Company had no outstanding warrant liability.

The following table sets forth a summary of changes in the fair value of the Company's preferred stock warrant liability which represents a recurring measurement that is classified within Level 3 of the fair value hierarchy wherein fair value is estimated using significant unobservable inputs (in thousands):

	Year ended December 31, 2013*
Beginning balance	$ 215
Change in fair value	440
Reclassification to equity	(655)
Ending balance	$ —

*These warrants were re-measured to fair value and then reclassified to additional paid-in capital on June 24, 2013.

The fair value of each warrant to purchase shares of the Company's Series B Preferred Stock was estimated using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year ended December 31, 2013*	
Fair value of underlying instrument	$ 0.95	
Expected volatility	82.0	%
Expected term (in years)	5.93	
Risk-free interest rate	1.1	%
Expected dividend yield	0.0	%

* Series B warrants were re-measured to fair value and then reclassified to additional paid-in capital on June 24, 2013.

9. Commitments and contingencies

On June 3, 2013, the Company entered into a nine-year building lease for approximately 43,600 square feet of space for its new corporate headquarters at 150 Second Street, Cambridge, Massachusetts, which commenced in December 2013. The lease originally had monthly lease payments of $0.2 million the first 12 months with annual rent escalations thereafter and provided a rent abatement of $0.2 million per month for the first six months. The Company has the option to extend this lease by an additional five years. As the Company obtained access to the newly leased space on July 22, 2013, this is considered the lease commencement date for accounting purposes, thus rent expense began on this date and is recognized on a straight-line basis over the term of the lease. In addition, the lease provided a contribution from the landlord towards the initial build-out of the space of up to $6.5 million. The Company capitalizes the leasehold improvements as property and equipment and records the landlord incentive payments received as deferred rent and amortizes these amounts as reductions to rent expense over the lease term. In accordance with the lease, the Company entered into a cash-collateralized irrevocable standby letter of credit in the amount of $1.3 million, naming the landlord as beneficiary. This letter of credit was reduced to $1.0 million during the third quarter of 2014 and may be further reduced to $0.8 million and $0.6 million upon the first and second anniversaries of the rent commencement date, respectively. The Company relocated into its new corporate headquarters in December 2013 and ceased use of its former facility during the first quarter of 2014. During the first quarter of 2014, the Company fully subleased its former facility, which decreased the rent abatement available under its new lease. The lease for the Company's former headquarters, located at 840 Memorial Drive, Cambridge, Massachusetts, expires on March 31, 2015.

On June 9, 2014, the Company amended its lease agreement to add an additional 9,869 square feet of space for its corporate headquarters at 150 Second Street, Cambridge, Massachusetts. The expansion increased the yearly lease payments by $0.6 million beginning in December 2014 with rent escalations thereafter. In addition, the lease amendment provides a contribution from the landlord towards the build-out of the additional space of up to $1.2 million.

As of December 31, 2014, future minimum commitments under facility operating leases were as follows (in thousands):

Years ended December 31,	Second Street Lease	Other Operating Leases	Total Lease Commitments
2015	$3,166	$ 486	$ 3,652
2016	3,261	231	3,492
2017	3,358	—	3,358
2018	3,460	—	3,460
2019	3,563	—	3,563
2020 and thereafter	11,344	—	11,344
Total minimum lease payments	$28,152	$ 717	$ 28,869

Rent expense is calculated on a straight-line basis over the term of the lease. Rent expense recognized under all operating leases, including additional rent charges for utilities, parking, maintenance, and real estate taxes was $4.3 million, $2.4 million and $0.8 million for the years ended December 31, 2014, 2013 and 2012, respectively.

The Company is party to various agreements, principally relating to licensed technology, that require future payments relating to milestones not met at December 31, 2014 and December 31, 2013 or royalties on future sales of specified products.

The Company enters into standard indemnification agreements in the ordinary course of business. Pursuant to the agreements, the Company indemnifies, holds harmless, and agrees to reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally the Company’s business partners or customers. The term of these indemnification agreements is generally perpetual any time after execution of the agreement. The maximum potential amount of future payments the Company could be

required to make under these indemnification agreements is unlimited. The Company has never incurred costs to defend lawsuits or settle claims related to these indemnification agreements.

The Company's wholly-owned subsidiary bluebird bio France – SARL participates in the French Crédit d'Impôt Recherche ("CIR") program which allows companies to monetize up to 30% of eligible research expenses. The Company received aggregate reimbursement of $1.4 million related to years 2011 through 2013. The Company recognized these amounts as reductions to research and development expense in the periods incurred. The years 2011 through 2013 are open and subject to examination. The Company has applied for but not yet received $0.9 million related to the year ended December 31, 2014 which are classified as current assets within the consolidated balance sheets as of December 31, 2014.

On June 30, 2014, the Company acquired Pregenen. The Company may be required to make up to an additional $135.0 million in future contingent cash payments to the former equityholders of Pregenen upon the achievement of certain preclinical, clinical and commercial milestones related to the Pregenen technology, of which $15.0 million relates to preclinical milestones, $20.1 million relates to clinical milestones and $99.9 million relates to commercial milestones. In accordance with accounting for business combinations guidance, contingent consideration liabilities are required to be recognized on the consolidated balance sheets at fair value. Estimating the fair value of contingent consideration requires the use of significant assumptions primarily relating to probabilities of successful achievement of certain preclinical, clinical and commercial milestones, the expected timing in which these milestones will be achieved and discount rates. The use of different assumptions could result in materially different estimates of fair value. See Note 4, "Fair value measurements," and Note 12, "Business combinations," for additional information.

10. Common stock and preferred stock

On June 18, 2013, the Company increased the authorized capital stock of the Company to 125,000,000 shares. Holders of common stock are entitled to one vote per share. Holders of common stock are entitled to receive dividends, if and when declared by the Company's Board of Directors, and to share ratably in the Company's assets legally available for distribution to the Company's shareholders in the event of liquidation. Holders of common stock have no preemptive, subscription, redemption or conversion rights.

The Company is authorized to issue 5,000,000 shares of preferred stock in one or more series and to fix the powers, designations, preferences and relative participating option or other rights thereof, including dividend rights, conversion rights, voting rights, redemption terms, liquidation preferences and the number of shares constituting any series, without any further vote or action by the Company's shareholders. As of December 31, 2014 and 2013, the Company had no shares of preferred stock issued or outstanding.

Reserved for future issuance

The Company has reserved for future issuance the following number of shares of common stock (in thousands):

	December 31, 2014
Options to purchase common stock	3,652
Restricted stock units	179
2013 Stock Option and Incentive Plan	465

Warrants to purchase common stock	177
Employee Stock Purchase Plan	238
Acquisition holdback (Note 12)	94
	4,805

11. Significant agreements

Celgene Corporation

Summary of the Collaboration Agreement

On March 19, 2013, the Company entered into a Master Collaboration Agreement (the “Collaboration Agreement”) with Celgene to discover, develop and commercialize potentially disease-altering gene therapies in oncology. The collaboration is focused on applying gene therapy technology to genetically modify a patient’s own T cells, known as chimeric antigen receptor, or CAR, T cells, to target and destroy cancer cells. Additionally, on March 19, 2013, the Company entered into a Platform Technology Sublicense Agreement (the “Sublicense Agreement”) with Celgene pursuant to which the Company obtained a sublicense to certain intellectual property from Celgene, originating under Celgene’s license from Baylor College of Medicine, for use in the collaboration.

Under the terms of the Collaboration Agreement, the Company received a $75.0 million up-front, non-refundable cash payment. The Company is responsible for conducting discovery, research and development activities through completion of Phase I clinical

studies, if any, during the initial term of the agreement, or three years. The collaboration is governed by a joint steering committee ("JSC") formed by an equal number of representatives from the Company and Celgene. The JSC will, among other activities, review the collaboration program, review and evaluate product candidates and approve regulatory plans. In addition to the JSC, the Collaboration Agreement provides that the Company and Celgene each appoint representatives to a patent committee, which is responsible for managing the intellectual property developed and used during the collaboration.

Prior to expiration of the initial term of the Collaboration Agreement, Celgene has two options to extend the term, through March 19, 2019, with the payment of significant extension fees. Separately, Celgene has an option to license an unlimited number of product candidates resulting from the collaboration during a period commencing upon execution of the Collaboration Agreement and continuing through a specified period following the completion of Phase I clinical studies for each individual product candidate. In the event such option is exercised, the Company would grant Celgene an exclusive worldwide license to develop and commercialize such product candidate. Upon exercise of the option to license a product candidate, Celgene is required to pay an option fee, which is subject to reduction if the Company elects to co-develop and co-promote such product candidate in the United States. For any product candidates licensed by Celgene, the Company may be responsible, at Celgene's election, to continue performing certain development activities contemplated as part of the collaboration plan. If Celgene does not exercise its option with respect to a product candidate prior to the expiration of the applicable option period (each a "declined product candidate"), then the Company has the right to develop the product candidate outside the scope of the collaboration, subject to a Celgene opt-in right to obtain a license to that declined product candidate for significant additional cash consideration. The opt-in right exists through a specified period following the completion of a pivotal study for the specific declined product candidate and functions in the same manner as the option to license any other product candidates resulting from the collaboration.

In addition, Celgene would be required to make certain milestone payments upon the achievement of specified clinical, regulatory and commercial events. For each product candidate that is licensed by Celgene, the Company would be eligible to receive per product up to $20.0 million in option fees, 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. Clinical milestone payments are triggered upon initiation of a defined phase of clinical research for a product candidate. Regulatory milestone payments are triggered upon approval to market a product candidate by the FDA or other global regulatory authorities. Commercial milestone payments are triggered upon the first commercial sale of an approved pharmaceutical product and when an approved pharmaceutical product reaches certain defined levels of net sales by the licensee or receives approval to be marketed by certain global regulatory authorities in a specified number of countries outside of the United States. In addition, to the extent any of the product candidates licensed by Celgene are commercialized, the Company would be entitled to receive tiered royalty payments ranging from the mid-single digits to mid-teens based on a percentage of net sales. Royalty payments 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. The Company is not eligible to receive either milestone payments or royalty payments unless and until Celgene exercises its option to license a product candidate resulting from the collaboration whereupon the parties will execute a license agreement, the terms of which are included as part of the collaboration arrangement.

Additionally, the Company may elect to co-develop and co-promote product candidates licensed by Celgene. If the Company elects to co-develop and co-promote a product candidate, then the parties would share equally in all costs incurred relating to the development, commercialization and manufacture of the product candidate within the United States and share equally in the profits generated by such product candidate in the United States. Additionally, if the Company elects to co-develop and co-promote a product candidate, then the option fees, milestones and royalties would decrease compared to those described above. Under this scenario, the Company would receive per product up to $10.0 million in option fees, 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. Clinical milestone payments are triggered upon initiation of a defined phase of clinical research for a product candidate. Regulatory milestone payments are triggered upon approval to market a product candidate by global regulatory

authorities. Commercial milestone payments are triggered when an approved pharmaceutical product reaches certain defined levels of net sales by the licensee or receives approval to be marketed by certain global regulatory authorities in a specified number of countries outside the United States. In addition, to the extent any of the product candidates licensed by Celgene and co-developed and co-promoted by the Company are commercialized, the Company would be entitled to receive tiered royalty payments ranging from the mid-single digits to mid-teens based on a percentage of net sales from sales generated outside of the United States. Royalty payments 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. The Company is not eligible to receive profit share payments, milestone payments or royalty payments unless and until Celgene exercises its option to license a product candidate resulting from the collaboration whereupon the parties will execute a co-development, co-promote and profit share agreement, the terms of which are included as part of the collaboration arrangement.

In the event Celgene elects to license a product candidate discovered and developed as part of the Collaboration Agreement, Celgene would be solely responsible for all costs and expenses of manufacturing and supplying any product candidates. Subject to customary back-up supply rights granted to Celgene, the Company has the sole right to manufacture or have manufactured supplies of vectors and associated payloads manufactured for incorporation into the associated product candidate. Celgene would reimburse the Company for the costs incurred to manufacture and supply such vectors and associated payloads, plus a modest mark-up. The

Company is not obligated to manufacture or have manufactured supplies of vectors and associated payloads for incorporation into an optioned product candidate unless and until Celgene exercises its option to license a product candidate resulting from the collaboration whereupon the parties will execute a separate manufacturing and supply agreement.

The Collaboration Agreement may be terminated by either the Company or Celgene, upon written notice, in the event of the other party's uncured material breach. Celgene may terminate the Collaboration Agreement for any reason upon written notice to the Company. If the Collaboration 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 Collaboration Agreement. In addition, if Celgene terminates the Collaboration Agreement as a result of a breach by the Company, then 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.

Call Option

During the initial three-year term of the collaboration and, if extended, during the first two-year extension term of the collaboration, in the event that the Company engages in a change in control transaction, including for such purposes a merger or consolidation of the Company or the sale of all or substantially all of the Company's assets, or if another person or entity or group of persons or entities acquires at least 50% of the Company's voting capital stock, then Celgene has the right, but not the obligation, to terminate the Collaboration Agreement and obtain perpetual, non-terminable, worldwide, exclusive, fully paid-up licenses to all, but not less than all, of the product candidates previously identified under the Collaboration Agreement (the "Call Option"). Under the Call Option, the product candidates to which Celgene would have the right to acquire licenses include any product candidate previously licensed out of the collaboration during the term of the collaboration, any product candidate for which the Company has exercised the right to co-develop and co-promote within the United States, any product candidate for which Celgene previously declined its option to obtain a license and any product candidate for which at least in vivo efficacy studies have been initiated or authorized by the JSC. The purchase price for such licenses would be based on the fair value of these rights received and obligations assumed determined pursuant to a binding arbitration process.

In addition, during the initial three-year term of the collaboration, but not during any extension term, in the event that Celgene exercises the Call Option, in addition to the right to acquire the fully paid-up licenses described above, Celgene would obtain a perpetual, non-terminable, worldwide, exclusive license to the Company's intellectual property to develop one or more CAR T cell products targeting one or more oncology associated target antigens for the remainder of the initial collaboration term. Following the initial collaboration term, the license to the Company's intellectual property is limited to target antigens identified by Celgene promptly following the initial collaboration term for which Celgene reasonably intends to develop CAR T cell products. There is no limit to the number of oncology-related target antigens Celgene may select under this license. Upon commercialization of any such product candidate so licensed by Celgene, Celgene would be obligated to pay the Company a specified milestone payment upon regulatory approval and a percentage of net sales as a royalty.

The Company concluded that the value of the Call Option is immaterial based primarily on the probability that the Call Option would become exercisable.

Accounting Analysis

The Company's arrangement with Celgene contains the following deliverables: (i) discovery, research and development services, (ii) participation on the JSC and (iii) participation on the patent committee. The Company has determined that the options to extend the term of the agreement and the options to license product candidates, including those related to Celgene's opt-in right for a declined product candidate, are substantive options. Celgene is not contractually obligated to exercise the options. Additionally, as a result of the uncertain outcome of the discovery,

research and development activities, the Company is at risk with regard to whether Celgene will exercise the options. Moreover, the Company has determined that the options are not priced at a significant and incremental discount. Accordingly, the options are not considered deliverables at the inception of the arrangement and the associated option fees are not included in allocable arrangement consideration. The Company has determined that the potential obligation to manufacture or have manufactured supplies of vectors and associated payloads for incorporation into an optioned product candidate is contingent upon Celgene exercising its option to license a product candidate resulting from the collaboration. Therefore, consistent with the treatment of the options to license product candidates, the Company's potential obligation under a manufacturing and supply agreement is not considered a deliverable at the inception of the arrangement and the associated fees are not included in allocable arrangement consideration.

The Company concluded that each of the three deliverables identified at the inception of the arrangement (discovery, research and development services, participation on the JSC and participation on the patent committee) has standalone value from the other undelivered elements. Additionally, the Collaboration Agreement does not include return rights related to the initial collaboration term. Accordingly, each deliverable qualifies as a separate unit of accounting.

The Company identified the allocable arrangement consideration as the $75.0 million up-front payment. The Company determined that each of the identified deliverables have the same period of performance (the three year initial term) and have the same pattern of revenue recognition, ratably over the period of performance. As a result, the $75.0 million arrangement consideration will be recognized over the three year initial term.

The Company evaluated all of the milestones that may be received in connection with Celgene's option to license a product candidate resulting from the collaboration. In evaluating if a milestone is substantive, the Company assesses whether: (i) the consideration is commensurate with either the Company's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the Company's performance to achieve the milestone, (ii) the consideration relates solely to past performance and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. All clinical and regulatory milestones are considered substantive on the basis of the contingent nature of the milestone, specifically reviewing factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the milestone as well as the level of effort and investment required. Accordingly, such amounts will be recognized as revenue in full in the period in which the associated milestone is achieved, assuming all other revenue recognition criteria are met. All commercial milestones will be accounted for in the same manner as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.

During the years ended December 31, 2014 and 2013, the Company recognized $25.0 million and $19.8 million, respectively, of revenue associated with its collaboration with Celgene related to the recognition of discovery, research and development services. As of December 31, 2014 and 2013, there was $30.7 million and $55.2 million of deferred revenue, respectively, related to the Company's collaboration with Celgene which is classified as current or non-current in the consolidated balance sheets based on the contractual term of the arrangement.

Association Française contre les Myopathies

In January 2011, the Company entered into a research funding agreement with the Association Française contre les Myopathies ("AFM"), a nonprofit organization dedicated to curing rare neuromuscular diseases and providing treatments to reduce the associated disabilities of such diseases. As part of the agreement, AFM funded the Company 1.0 million Euros to be used to advance the Company's research, process development, manufacturing, preclinical development, and clinical development in gene therapy for beta-hemoglobinopathies in ß-thalassemia and/or in Sickle Cell Disease.

The funding, or a portion thereof depending on timing, shall be repaid to AFM upon any of the following events: (i) upon out-licensing or sale of the program, (ii) upon obtaining the first product authorization for the market, or (iii) upon sale of the Company, provided that the development is active at the time of such sale. The agreement is for a period of four years. The Company believes that repayment of the funds paid under the agreement is remote at the date of the agreement, December 31, 2014 or December 31, 2013. The Company recognizes the revenue under this arrangement on a straight-line basis over the term of the agreement. The Company will reassess the probability of repayment at the end of each reporting period.

12. Business combinations

On June 30, 2014, the Company completed its acquisition of Pregenen, a privately-held biotechnology company, upon which Pregenen became a wholly-owned subsidiary. As a result, the Company obtained gene editing and cell signaling technology with a broad range of potential therapeutic applications.

Under the terms of the Stock Purchase Agreement, the Company purchased all of Pregenen's outstanding capital stock in exchange for 405,401 unregistered shares of common stock and $5.1 million in cash. The consideration for the transaction also includes an additional 94,117 shares of common stock that will be held for a period of 18 months after the acquisition and may be used to settle certain claims for indemnification for breaches or inaccuracies in Pregenen's representations and warranties, covenants, and agreements and an additional 2,119 shares relating to a working capital adjustment. The Stock Purchase Agreement also provides for up to $135.0 million in future contingent cash payments upon the achievement of certain preclinical, clinical and commercial milestones related to the Pregenen technology, of which $15.0 million relates to preclinical milestones, $20.1 million relates to clinical milestones and $99.9 million relates to commercial milestones.

The acquisition-date fair value of the purchase consideration is as follows (in thousands):

Cash	$5,093
Common stock	19,348
Contingent consideration	6,550
Total purchase consideration	$30,991

Common stock in the table above is comprised of $15.6 million in common stock transferred, $3.6 million in common stock that will be held back for a period of 18 months and $0.1 million related to a working capital adjustment.

The transaction was accounted for as a business combination under the acquisition method of accounting. Accordingly, the tangible and identifiable intangible assets acquired and liabilities assumed were recorded at estimated fair value as of the date of acquisition, with the remaining consideration transferred recorded as goodwill.

The purchase price allocation has been finalized and the following table summarizes the estimated fair value of the assets acquired and liabilities assumed at the date of acquisition (in thousands):

	Acquisition date fair value
Cash	$ 420
Gene editing platform intangible asset	30,100
Goodwill	13,128
Other assets acquired	111
Total assets acquired	43,759
Deferred tax liabilities	11,797
Other liabilities assumed	971
Total liabilities assumed	12,768
Net assets acquired	$ 30,991

The fair value of the gene editing platform intangible asset was determined using a relief from royalty approach, including assumptions of projected revenues and royalty rate in addition to a discount rate of 15.5% applied to the projected cash flows. The Company considers the intangible asset acquired to be developed technology, as at the date of the acquisition it could be used the way it is intended to be used in certain ongoing research and development activities. The Company believes the assumptions are representative of those a market participant would use in estimating fair value. The gene editing platform intangible asset will be amortized to research and development expense over its expected useful life of approximately eight years.

Amortization expense for the gene editing platform intangible asset was $1.9 million for the year ended December 31, 2014 and accumulated amortization as of December 31, 2014 was $1.9 million. The estimated amortization of intangible assets for the year ended December 31, 2015 and for each of the five succeeding years and thereafter is as follows (in thousands):

2015	$3,763
2016	3,763
2017	3,763
2018	3,763
2019	3,763
2020 and thereafter	9,404
Total	$28,219

The deferred tax liabilities of $11.8 million primarily relate to the tax impact of future amortization or impairments associated with the identified intangible asset, which is not deductible for tax purposes. See Note 15 “Income taxes,” for additional information.

Goodwill is calculated as the difference between the acquisition-date fair value of the consideration transferred and the fair values of the assets acquired and liabilities assumed and is not expected to be deductible for income tax purposes. Goodwill is recorded as an indefinite-lived asset and is not amortized but tested for impairment on an annual basis or when indications of impairment exist. Among the factors which resulted in goodwill for the Pregenen acquisition was the opportunity to recognize synergies with the Company’s existing gene insertion platform and deferred tax liabilities recognized in connection with the acquisition.

The Company incurred a total of $0.2 million in transaction costs in connection with the acquisition, which were included in general and administrative expenses within the consolidated statements of operations and comprehensive loss for the year ended December 31, 2014.

In connection with the acquisition, the Company issued 3,267 shares of common stock to a former consultant of Pregenen and recognized $0.2 million of expense within general and administrative expenses in the consolidated statements of operations and comprehensive loss for the year ended December 31, 2014.

13. Stock-based compensation

On June 3, 2013, the Company's board of directors adopted its 2013 Stock Option and Incentive Plan ("2013 Plan"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO on June 24, 2013. The 2013 Plan replaces the 2010 Stock Option and Grant Plan ("2010 Plan").

The 2013 Plan allows for the granting of incentive stock options, non-qualified stock options, restricted stock units and restricted stock awards to the Company's employees, members of the board of directors, and consultants of the Company. The Company initially reserved 955,000 shares of its common stock for the issuance of awards under the 2013 Plan. The 2013 Plan provides that the number of shares reserved and available for issuance under the 2013 Plan will automatically increase each January 1, beginning on January 1, 2014, by four percent of the outstanding number of shares of common stock on the immediately preceding December 31 or such lesser number of shares as determined by the Company's compensation committee.

Any options or awards outstanding under the Company's previous stock option plans, including both the 2010 Plan and the Second Amended and Restated 2002 Employee, Director and Consultant Stock Plan ("2002 Plan"), at the time of adoption of the 2013 Plan remain outstanding and effective. The shares of common stock underlying any awards that are forfeited, canceled, repurchased, expire or are otherwise terminated (other than by exercise) under the 2002 Plan and 2010 Plan are added to the shares of common stock available for issuance under the 2013 Plan. As of December 31, 2014, the total number of common stock that may be issued under all equity award plans is 464,530.

The Company does not currently hold any treasury shares. Upon stock option exercise, the Company issues new shares and delivers them to the participant.

Stock-based compensation expense

The Company recognized stock-based compensation expense totaling $10.8 million, $6.5 million and $0.8 million during the years ended December 31, 2014, 2013 and 2012, respectively. Share-based compensation expense recognized by award type is as follows (in thousands):

	Year ended December 31,		
	2014	2013	2012
Stock options	$9,487	$6,399	$742
Restricted stock awards	52	92	80
Restricted stock units	1,158	—	—
Employee stock purchase plan	66	—	—
	$10,763	$6,491	$822

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

	Year ended December 31,		
	2014	2013	2012
Expected volatility	82.3 %	82.0 %	79.6 %

Expected term (in years)	6.0		6.1		6.1	
Risk-free interest rate	1.8	%	1.1	%	1.0	%
Expected dividend yield	0.0%		0.0%		0.0%	

The intrinsic value of options exercised during the years ended December 31, 2014, 2013, and 2012, was $41.4 million, $3.9 million and $0, respectively.

The weighted-average fair values of options granted during 2014, 2013 and 2012 was $18.53, $7.36 and $1.51, respectively.

The aggregate fair value of restricted stock awards that vested during the years ended December 31, 2014, 2013 and 2012, based on the estimated fair value of the underlying stock on the day of vesting was $1.9 million, $1.5 million and $0.1 million, respectively.

As of December 31, 2014, there was $22.1 million and $3.9 million of unrecognized compensation expense related to unvested stock options and restricted stock units, respectively, that is expected to be recognized over a weighted-average period of 2.9 and 1.5 years.

During the year ended December 31, 2014, the Company issued 2,000 shares of restricted common stock in exchange for consulting services. The shares vested upon issuance and the Company recognized $0.1 million of expense related to the services provided.

During the year ended December 31, 2014, 123,263 options held by former employees were modified to accelerate vesting and extend the period in which the employees were allowed to exercise the vested options. The modification was valued using a Black-Scholes option valuation model and the Company accounted for the $0.6 million of incremental value within general and administrative expenses.

Restricted common stock

A summary of the Company's restricted stock awards activity and related information is as follows:

	Shares	Weighted-average grant date fair value
Unvested balance at December 31, 2013	68,822	$ 0.95
Granted	—	—
Vested	(68,822)	0.95
Forfeited	—	—
Unvested balance at December 31, 2014	—	$ —

Restricted stock units

A summary of the Company's restricted stock unit activity and related information is as follows:

	Shares	Weighted-average grant date fair value
Unvested balance at December 31, 2013	—	$ —
Granted	185,850	30.47
Vested	—	—
Forfeited	(6,430)	30.47
Unvested balance at December 31, 2014	179,420	$ 30.47

Stock options

The following table summarizes the stock option activity under the Plan:

	Shares	Weighted-average exercise price	Weighted-average contractual	Aggregate intrinsic

		per share	life (in years)	value (a)
				(in thousands)
Outstanding at December 31, 2013	3,957,673	$ 5.21		
Granted	1,188,060	$ 26.80		
Exercised	(1,313,031)	$ 3.95		
Canceled or forfeited	(180,465)	$ 12.98		
Outstanding at December 31, 2014	3,652,237	$ 12.30	8.1	$ 290,049
Exercisable at December 31, 2014	1,251,045	$ 4.37	7.2	$ 109,283
Vested and expected to vest at December 31, 2014	3,597,828	$ 12.41	8.1	$ 285,358

(a) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the estimated fair value of the common stock for the options that were in the money at December 31, 2014.

Note receivable

In November 2010, the Company received a non-recourse note from its Chief Executive Officer (“CEO”) in exchange for the purchase of 329,256 shares of restricted stock. Interest accrued on the note on an annual basis at a rate of four percent. In May 2013, prior to the initial filing of the registration statement in connection with the Company’s IPO, the CEO repaid the note in full plus all

accrued interest. The Company recorded stock-based compensation expense in connection with this restricted stock award of $0.1 million, $0.1 million and $0.1 million for the years ended December 31, 2014, 2013 and 2012, respectively.

Employee Stock Purchase Plan

On June 3, 2013, the Company's board of directors adopted its 2013 Employee Stock Purchase Plan ("2013 ESPP"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO on June 24, 2013. The 2013 ESPP authorizes the initial issuance of up to a total of 238,000 shares of the Company's common stock to participating employees. The first offering period under the 2013 ESPP opened on August 1, 2014.

14. 401(k) Savings plan

In 1997, the Company established a defined-contribution savings plan under Section 401(k) of the Internal Revenue Code ("the 401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants to defer a portion of their annual compensation on a pretax basis. The Company has not made any contributions to the 401(k) Plan for the three years ended December 31, 2014.

15. Income taxes

The components of loss before income taxes were as follows (in thousands):

	Year ended December 31,		
	2014	2013	2012
U.S.	$(61,118)	$(26,018)	$(23,700)
Foreign	612	697	30
Total	$(60,506)	$(25,321)	$(23,670)

The benefit for income taxes were as follows (in thousands):

	Year ended December 31,		
	2014	2013	2012
Current			
Federal	$—	$ —	$ —
State	1	—	—
Foreign	—	—	—
Deferred			—

Federal	(9,390)	—	—
State	(2,408)	—	—
Foreign	—	—	—
Total income tax benefit	$(11,797)	$ —	$ —

A reconciliation of income tax benefit computed at the statutory federal income tax rate to the Company's effective income tax rate benefit as reflected in the financial statements is as follows:

	Year ended December 31,		
	2014	2013	2012
Federal income tax expense at statutory rate	34.0 %	34.0 %	34.0 %
State income tax, net of federal benefit	4.0 %	4.5 %	4.4 %
Permanent differences	(3.2 %)	(0.6 %)	(0.8 %)
Research and development credit	25.7 %	6.0 %	0.8 %
Other	0.0 %	0.0 %	0.6 %
Change in valuation allowance	(41.0%)	(43.9%)	(39.0%)
Effective income tax rate benefit	19.5 %	0.0 %	0.0 %

For the year ended December 31, 2014, the Company recognized an income tax benefit of $11.8 million or 19.5%. The Company recorded a non-recurring tax benefit of $11.8 million due to the release of a portion of the valuation allowance due to taxable

temporary differences available as a source of income to realize certain pre-existing deferred tax assets as a result of the acquisition of Pregenen. Excluding the impact of this item, the Company's overall tax provision and effective tax rate would be zero.

The Company did not recognize any tax benefit for the years ended December 31, 2013 and December 31, 2012 as the Company was subject to a full valuation allowance.

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are comprised of the following (in thousands):

	Year ended December 31,	
	2014	2013
Deferred tax assets:		
U.S. net operating loss carryforwards	$33,767	$11,010
Foreign net operating loss carryforwards	899	659
Tax credit carryforwards	23,274	3,638
Capitalized research and development expenses, net	1,372	1,837
Deferred revenue	12,050	21,830
Accruals and other	7,552	4,177
Total deferred tax assets	78,914	43,151
Intangible assets	(11,084)	-
Fixed assets	(2,526)	(2,596)
Less valuation allowance	(65,304)	(40,555)
Net deferred taxes	$—	$—

A valuation allowance is recorded against deferred tax assets if it is more likely than not that some or all of the deferred tax assets will not be realized. Due to the uncertainty surrounding the realization of the favorable tax attributes in future tax returns, the Company has recorded a full valuation allowance against the Company's otherwise recognizable net deferred tax assets. The Company has allocated its valuation allowance in accordance with the provisions of ASC 740, which resulted in a current deferred tax asset of $1.9 million and a non-current deferred tax liability of $1.9 million as of December 31, 2014. The valuation allowance increased on a net basis by approximately $24.7 million during the year ended December 31, 2014 due primarily to net operating losses and tax credit carryforwards.

As of December 31, 2014, 2013 and 2012, the Company had U.S. federal net operating loss carryforwards of approximately $130.0 million, $30.3 million and $62.6 million, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2034. As of December 31, 2014, 2013 and 2012, the Company also had U.S. state net operating loss carryforwards of approximately $115.5 million, $13.3 million and $52.3 million, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2034. At December 31, 2014, $42.1 million and $42.1 million of federal and state net operating losses, respectively, relate to excess equity based compensation tax deductions, the benefits for which will be recorded to additional paid-in capital when recognized through a reduction of cash taxes paid. At December 31, 2014, 2013 and 2012, the Company also had approximately $2.7 million, $2.0 million and $1.8 million, respectively, of foreign net operating loss carryforwards which may be available to offset future income tax liabilities; these carryforwards do not

expire.

As of December 31, 2014, 2013 and 2012, the Company had federal research and development and orphan drug tax credit carryforwards of approximately $22.0 million, $2.7 million and $1.3 million, respectively, available to reduce future tax liabilities which expire at various dates through 2034. As of December 31, 2014, 2013 and 2012, the Company had state credit carryforwards of approximately $2.0 million, $1.4 million and $0.9 million, respectively, available to reduce future tax liabilities which expire at various dates through 2029.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception which it believes has resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2014, 2013 and 2012, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's consolidated statements of operations and comprehensive loss.

For all years through December 31, 2014, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

The Company or one of its subsidiaries files income tax returns in the United States, and various state and foreign jurisdictions. The federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2011 through December 31, 2014. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service, state or foreign tax authorities to the extent utilized in a future period.

16. Net loss per share

The following common stock equivalents were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect (in thousands):

	Year ended December 31,		
	2014	2013	2012
Warrants	177	338	440
Outstanding stock options	3,652	3,958	2,201
Unvested restricted stock	—	69	155
Restricted stock units	179	—	—
ESPP shares	6	—	—
Acquisition holdback (Note 12)	94	—	—
Preferred stock	—	—	16,389
	4,108	4,365	19,185

17. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2014 and 2013. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2014				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share data)				
Total revenue	$6,335	$6,335	$6,365	$6,386	$25,421
Total operating expenses	17,003	19,669	23,375	26,000	86,047
Loss from operations	(10,668)	(13,334)	(17,010)	(19,614)	(60,626)
Net loss	(10,609)	(1,526)(1)	(17,030)	(19,544)	(48,709)
Net loss per share applicable to common stockholders - basic and diluted	$(0.44)	$(0.06)	$(0.61)	$(0.67)	$(1.83)

	2013				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share data)				
Total revenue	$1,127	$6,334	$6,385	$6,335	$20,181
Total operating expenses	7,608	10,528	12,542	14,450	45,128
Loss from operations	(6,481)	(4,194)	(6,157)	(8,115)	(24,947)
Net loss	(6,544)	(4,583)	(6,113)	(8,081)	(25,321)
Net loss per share applicable to common stockholders - basic and diluted	$(19.94)	$(2.13)	$(0.26)	$(0.34)	$(2.02)

(1) During the second quarter of 2014, the Company recorded an income tax benefit of $11.8 million in connection with the acquisition of Pregenen completed in June 2014. See Note 12, “Business Combinations” for additional information.

18. Subsequent events

The Company has evaluated all events or transactions that occurred after December 31, 2014. In the judgment of management, there were no material events that impacted the consolidated financial statements or disclosures.

SIGNATURES

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

bluebird bio, Inc.

By: /s/ Nick Leschly
Nick Leschly
President, Chief Executive Officer and Director

SIGNATURES AND POWER OF ATTORNEY

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

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

Name	Title	Date
/s/ Nick Leschly Nick Leschly	President, Chief Executive Officer and Director (Principal Executive Officer)	February 25, 2015
/s/ James M. DeTore James M. DeTore	Chief Financial Officer and Treasurer (Principal Financial Officer)	February 25, 2015
/s/ Eric Sullivan Eric Sullivan	Senior Director, Finance (Principal Accounting Officer)	February 25, 2015
/s/ Robert I. Tepper, M.D. Robert I. Tepper, M.D.	Director	February 25, 2015
/s/ Steven Gillis, Ph.D. Steven Gillis, Ph.D.	Director	February 25, 2015
/s/ Daniel S. Lynch Daniel S. Lynch	Director	February 25, 2015
/s/ James Mandell, M.D. James Mandell, M.D.	Director	February 25, 2015

/s/ John M. Maraganore, Ph.D. John M. Maraganore, Ph.D.	Director	February 25, 2015
/s/ Wendy L. Dixon, Ph.D. Wendy L. Dixon, Ph.D.	Director	February 25, 2015
/s/ David P. Schenkein, M.D. David P. Schenkein, M.D.	Director	February 25, 2015
/s/ Mark Vachon Mark Vachon	Director	February 25, 2015

Exhibit Index

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
2.1	Stock Purchase Agreement by and between the Registrant and Precision Genome Engineering, Inc.	8-K	001-35966	2.1	June 30, 2014
3.1	Amended and Restated Certificate of Incorporation of the Registrant	8-K	001-35966	3.1	June 24, 2013
3.2	Amended and Restated By-laws of the Registrant	8-K	001-35966	3.2	June 24, 2013
4.1	Specimen Common Stock Certificate	S-1/A	333-188605	4.1	June 4, 2013
4.2	Form of Common Stock Warrant	S-1/A	333-188605	4.2	May 14, 2013
4.3	Form of Series A-1 Preferred Stock Warrant	S-1/A	333-188605	4.3	May 14, 2013
4.4	Form of Series B Preferred Stock Warrant	S-1/A	333-188605	4.4	May 14, 2013
4.5	Amended and Restated Investors' Rights Agreement, dated as of July 23, 2012, by and among the Registrant and the Investors listed therein.	S-1/A	333-188605	4.5	May 14, 2013
4.6	Amendment to Amended and Restated Investors' Rights Agreement, dated as of July 8, 2014, by and among the Registrant and the Investors listed therein.	10-Q	001-35966	4.6	August 12, 2014
10.1	Second Amended and Restated 2002 Employee, Director and Consultant Plan, as amended, and forms of award agreement thereunder	S-1/A	333-188605	10.1	May 14, 2013
10.2	2010 Stock Option and Grant Plan, as amended, and forms of award agreement thereunder	S-1/A	333-188605	10.2	May 14, 2013
10.3	2013 Stock Option and Incentive Plan and forms of award agreement thereunder	S-1/A	333-188605	10.3	June 4, 2013
10.4	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1/A	333-188605	10.4	May 14, 2013
10.5	Amended and Restated Lease Agreement, dated May 18, 2007, by and between the Registrant and	10-Q	001-35966	10.1	November 14, 2013

	Rivertech Associates II, LLC, as amended				
10.6†	Patent License Agreement, dated December 11, 1996, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc., successor-in-interest to Innogene Pharmaceuticals Inc.) and Massachusetts Institute of Technology, as amended	S-1/A	333-188605	10.6	May 14, 2013
10.7†	Patent and Know-How License Agreement No. 07554F30, dated May 14, 2009, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc.) and INSERM-TRANSFERT, as amended	S-1/A	333-188605	10.7	May 14, 2013
10.8†	License Agreement, dated September 13, 2011, by and between the Registrant and Institut Pasteur, as amended	S-1/A	333-188605	10.8	May 14, 2013
10.9†	Amendment No. 3 to License Agreement, dated September 10, 2013, by and between the Registrant and Institut Pasteur	10-Q	001-35966	10.2	November 14, 2013
10.10†	License Agreement, dated December 7, 2011, by and between the Registrant and Research Development Foundation	S-1/A	333-188605	10.9	May 14, 2013
10.11†	Novation Agreement, dated April 2, 2012, by and between the Registrant and The Board of Trustees of the Leland Stanford Junior University	S-1/A	333-188605	10.10	May 14, 2013
10.12†	Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated March 19, 2013	S-1/A	333-188605	10.11	May 14, 2013

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
10.13	Amended and Restated Employment Agreement by and between the Registrant and Nick Leschly	S-1/A	333-188605	10.12	June 4, 2013
10.14	Amended and Restated Employment Agreement by and between the Registrant and Jeffrey T. Walsh	S-1/A	333-188605	10.13	June 4, 2013
10.15	Amended and Restated Employment Agreement by and between the Registrant and Mitch Finer	S-1/A	333-188605	10.14	June 4, 2013
10.16	Amended and Restated Employment Agreement by and between the Registrant and David M. Davidson, M.D.	S-1/A	333-188605	10.15	June 4, 2013
10.17	Offer Letter, dated September 27, 2011 by and between the Registrant and Linda Bain	S-1/A	333-188605	10.16	June 4, 2013
10.18	Employment Agreement, dated February 3, 2014, by and between the Registrant and Jason F. Cole	10-Q	001-35966	10.18	May 13, 2014
10.19	Employment Agreement, dated October 20, 2014, by and between the Registrant and James DeTore	8-K	001-35966	10.1	November 10, 2014
10.20	Offer Letter, dated October 14, 2013, by and between the Registrant and Eric Sullivan	10-Q	001-35966	10.19	May 13, 2014
10.21	2013 Employee Stock Purchase Plan	S-1/A	333-188605	10.17	June 4, 2013
10.22	Executive Cash Incentive Bonus Plan	S-1/A	333-188605	10.18	May 14, 2013
10.23	Lease, dated June 3, 2013, by and between the Registrant and 150 Second Street, LLC, as amended	S-1/A	333-188605	10.19	June 4, 2013
10.24	Lease Amendment, dated November 15, 2013, by and between the Registrant and 150 Second Street, LLC, as amended	10-K	001-35966	10.19	March 5, 2014
10.25	Lease Amendment, dated June 9, 2014, by and between the Registrant and 150 Second Street, LLC, as amended	10-Q	011-35966	10.24	August 12, 2014
21.1	Subsidiaries of the Registrant	10-Q	011-35966	21.1	August 12, 2014
23.1	Consent of Ernst & Young LLP	—	—	—	Filed herewith
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.	—	—	—	Filed herewith

31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.	—	—	—	Filed herewith
32.1	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	—	—	—	Furnished herewith
101	The following materials from the Company's Annual Report on Form10-K for the year ended December 31, 2014, formatted in XBRL (eXtensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations and Comprehensive Loss, (iii) Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit), (iv) Consolidated Statements of Cash Flows and (v) Notes to Consolidated Financial Statements.	—	—	—	Filed herewith

†Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been submitted separately to the SEC.