bluebird bio, Inc.
Form S-1
May 14, 2013
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As filed with the Securities and Exchange Commission on May 14, 2013

Registration No. 333-

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-1

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

bluebird bio, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**2836**	**13-3680878**
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

840 Memorial Drive, 4th Floor

Cambridge, MA 02139

(617) 491-5601

(Address, including zip code, and telephone number, including area code, of registrant s principal executive offices)

Nick Leschly

President and Chief Executive Officer

bluebird bio, Inc.

840 Memorial Drive, 4th Floor

Cambridge, MA 02139

(617) 491-5601

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

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Approximate date of commencement of proposed sale to public: As soon as practicable after this Registration Statement is declared effective.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. ¨

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

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

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

smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Proposed maximum aggregate offering price(1)	Amount of registration fee(2)
Common stock, $0.01 par value	$86,250,000	$11,764.50

(1) Includes offering price of shares that the underwriters have the option to purchase to cover overallotments, if any. Estimated solely for the purpose of calculating the registration fee in accordance with Rule 457(o) of the Securities Act of 1933, as amended.

(2) Calculated pursuant to Rule 457(o) based on an estimate of the proposed maximum aggregate offering price.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

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The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities, and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated May 14, 2013

Prospectus

shares

Common stock

This is an initial public offering of common stock by bluebird bio, Inc. We are selling shares of common stock. The estimated initial public offering price is between $ and $ per share.

Prior to this offering, there has been no public market for our common stock. We have applied for listing of our common stock on The Nasdaq Global Market under the symbol BLUE.

We are an emerging growth company under applicable Securities and Exchange Commission rules and will be subject to reduced public company reporting requirements.

	Per share	Total
Initial public offering price	$	$
Underwriting discounts and commissions	$	$
Proceeds to bluebird bio, before expenses	$	$

We have granted the underwriters an option for a period of 30 days to purchase up to additional shares of common stock.

Investing in our common stock involves a high degree of risk. See Risk factors beginning on page 13.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed on the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock to investors on or about , 2013.

J.P. Morgan **BofA Merrill Lynch**

Cowen and Company

Canaccord Genuity **Wedbush PacGrow Life Sciences**

, 2013

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We have not authorized anyone to provide you with information other than that contained in this prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give to you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

No action is being taken in any jurisdiction outside the United States to permit a public offering of our common stock or possession or distribution of this prospectus in that jurisdiction. Persons who come into possession of this prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus applicable to that jurisdiction.

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Prospectus summary

Overview

We are a clinical-stage biotechnology company focused on transforming the lives of patients with severe genetic and orphan diseases using gene therapy. Many diseases have a genetic aspect whereby a mutated gene linked to a disease is passed down from generation to generation. Genes produce proteins that perform a vast array of functions within all living organisms, through a process called gene expression. 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 seeks to introduce a functional copy of the defective gene into a patient s own cells, a process called gene transfer. Gene therapy thereby 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 delivered and incorporated into a patient s cells through a delivery system called a vector, which are most commonly based on naturally-occurring viruses that have been modified to take advantage of the virus natural ability to introduce genes into cells. However, unlike naturally-occurring viruses, which replicate following infection of a target cell and have the capacity to infect new cells, viral vectors are modified to be non-replicating by deleting that portion of the viral genome responsible for replication. Gene transfer using a viral vector is called transduction and the resulting gene-modified cells are described as transduced cells.

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 suggest that the time is now for gene therapy to emerge as an 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 orphan diseases. We have assembled extensive expertise in viral vector design, manufacturing and gene transfer, a broad intellectual property estate, an experienced management team and a world-class group of scientific advisors and key opinion leaders. We refer to our viral vector and gene transfer technology and know-how as our gene therapy platform.

We and our scientific collaborators have generated what we believe is human proof-of-concept data for our gene therapy platform in two underserved diseases, each of which has been granted orphan drug status by U.S. and European regulatory authorities. We expect to initiate in late 2013 a Phase II/III clinical 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. We also expect to initiate in mid-2013 Phase I/II clinical studies in the United States and Europe of our next most advanced product candidate, LentiGlobin, to evaluate its safety and efficacy in subjects with ß-thalassemia major and, in the European clinical study, sickle cell disease, or SCD, which are rare, hereditary blood disorders that often lead to severe anemia and shortened lifespans. In addition,

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in March 2013, we announced a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel, disease-altering gene therapies in oncology.

Our gene therapy platform and process

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, a concept we refer to as the industrialization of gene therapy.

We believe our lentiviral vectors have certain advantages over other viral vectors used for gene therapy, including the ability to achieve long-term, sustained expression of the modified gene and reduced risk of insertional oncogenesis, the process whereby the corrected gene inserted near a gene that is important in cell growth or division, and this insertion results in uncontrolled cell division also known as cancer. Although our initial focus is in CCALD, ß-thalassemia and SCD, we believe our gene therapy platform has broad therapeutic potential in a variety of indications. We believe our vectors can be used to introduce virtually any gene and have the potential to be manufactured on a commercial scale reproducibly and reliably, as each new vector is produced using substantially the same process. We also take advantage of lentivirus ability to transduce HSCs more efficiently than other vectors, such as those derived from another virus used in gene therapy approaches, called adeno-associated virus, or AAV, which gives us the potential to address diseases in a variety of cell lineages that are derived from HSCs, such as microglia (useful for CCALD), red blood cells (useful for ß-thalassemia and SCD), T cells (useful for cancer and immunology) and others.

Based in part on these features, we believe our gene therapy platform 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.

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, thus mitigating against the uncertainty of the disease biology.

Existing practice of transplanting cells from a donor provides proof-of-concept for our approach. Clinical proof-of-concept already exists for the diseases we are targeting via

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allogeneic hematopoietic stem cell transplant, or HSCT, an approach of treating a patient with HSCs contributed by a donor that contain a functioning copy of the gene underlying the 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, or GVHD.

We modify our target cells outside the patient s body. By inserting the new functional deoxyribonucleic acid, or DNA, into the cells outside the patient s body, or *ex vivo*, thereby creating a gene-modified cell, 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, providers and payors. Given the potentially dramatic clinical and life-long benefits anticipated from such therapies delivered through a single administration, we believe the value proposition for patients, families, providers and payors would be significant.

Our product candidate pipeline

Below is a summary of key information on our development programs:

* The Phase II/III ALD-102 Study is our first clinical study of our current Lenti-D viral vector and product candidate. See Business Our Lenti-D product candidate.

** The Phase I/II HGB-205 and HGB-204 Studies are our first clinical studies of our current LentiGlobin viral vector and product candidate. See Business Our LentiGlobin product candidate.

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Our Lenti-D product candidate

Our most advanced product candidate is called Lenti-D, which we are developing initially to treat patients with CCALD, a rare, hereditary neurological disorder affecting young boys that is often fatal. CCALD is caused by mutations in the ABCD1 gene, which encodes for a protein called the ALD protein, or ALDP, which in turn plays a critical role in the breakdown and metabolism of very long-chain fatty acids, or VLCFA. Without functional ALDP, VLCFA accumulate in cells, including neural cells, which causes damage to the myelin sheath, a protective and insulating membrane that surrounds nerve cells in the brain. CCALD is characterized by progressive destruction of myelin, leading to severe loss of neurological function and eventual death. The incidence rate for adrenoleukodystrophy, or ALD, the superset of CCALD, is approximately one in 20,000 newborn males, and the U.S. National Institute of Health, or NIH, estimates a prevalence of one in 20,000; CCALD accounts for about 30-40% of patients diagnosed with ALD.

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. HSCs derived from the patient s own body are called autologous HSCs. We refer to autologous HSCs that have been modified to carry the functional copy of the ABCD1 gene as the final Lenti-D drug product, or our Lenti-D product candidate.

We performed a non-interventional retrospective data collection study, called the ALD-101 Study, from a total of 136 CCALD patients to assess the course of disease in patients who were left untreated and patients who received allogeneic HSCT. 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. We believe the ALD-101 Study is the most comprehensive natural history study ever conducted to characterize clinical outcomes in CCALD. Our analysis identified the Neurological Function Score, or NFS, Loes Score and gadolinium enhancement as the three most common cognitive, behavioral, functional and radiological modalities utilized to assess patients with CCALD. A comparison of data from treated and untreated patient cohorts in this data collection study provided a framework with which to correlate patterns in these modalities with the eventual stabilization or progression of disease in these patients. We believe the results of this study support our approach of using autologous, gene-modified HSCs to treat CCALD, especially in light of several significant safety concerns commonly associated with the current standard of care, allogeneic HSCT. Results from a Phase I/II study in four patients with CCALD conducted by our scientific collaborators in France with an earlier generation lentiviral vector supplied by a third party provide additional proof-of-concept support for our approach, and were helpful in the design of our own trials to evaluate the efficacy and safety of Lenti-D.

In April 2013, the U.S. Food and Drug Administration, or the FDA, informed us that the Investigational New Drug application, or IND, we filed in March 2013 for a Phase II/III clinical study to evaluate our Lenti-D product candidate in preserving neurological function and stabilizing cerebral demyelination in subjects with CCALD, which we refer to as the ALD-102 Study, is now active. Up to 15 patients will be enrolled to obtain at least 12 evaluable subjects that will be followed over a 24-month period for the onset of major functional disabilities, or MFDs, and other key assessments of disease progression. We expect to initiate the ALD-102 Study in the United States in late 2013. If successful, we believe the results of this study could support

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submission of a Biologics License Application, or BLA, and a Marketing Authorization Application, or MAA, filing for our Lenti-D product candidate; however, there can be no assurance that regulatory agencies will not require one or more additional clinical studies prior to granting regulatory approval.

Our LentiGlobin product candidate

Our next most advanced product candidate is called LentiGlobin, which we are developing to treat patients with ß-thalassemia and SCD. ß-thalassemia is a rare hereditary blood disorder caused by a genetic abnormality of the ß-globin gene resulting in defective red blood cells. Symptoms of ß-thalassemia can include severe anemia, splenomegaly, marrow expansion, bone deformities and iron overload in major organs. The total annual incidence of symptomatic individuals is estimated at one in 100,000 throughout the world and one in 10,000 in the European Union. 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. SCD is characterized by anemia, vaso-occlusive 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. 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.

Our approach involves the insertion of a single codon variant of the normal ß-globin gene, referred to as T87Q, into the patient s own HSCs via an HIV-1 based lentiviral vector to restore expression of the ß-globin protein required for hemoglobin production. The codon variant is also used as a biomarker to quantify expression levels of ß-globin protein derived from the vector ($ß^{A-T87Q}$-globin), and provides strong anti-sickling properties in the context of SCD. We refer to the gene-modified HSCs as the final LentiGlobin drug product, or our LentiGlobin product candidate.

In a Phase I/II study of patients with ß-thalassemia major being conducted by our scientific collaborators in France with an earlier generation of our LentiGlobin vector called HPV569, data have provided initial evidence of transfusion independence following treatment with gene modified HSCs. Going forward, we plan to use our new LentiGlobin vector for our studies based on higher transduction efficiency and expression of ß-globin protein in target cells as compared to the HPV569 vector. We expect to initiate this study in France the first half of 2013 using a revised clinical protocol based on the use of LentiGlobin instead of HPV569. This Phase I/II continuation study, which we refer to as the HGB-205 Study, will enroll up to seven additional subjects with ß-thalassemia major or SCD to evaluate transfusion requirements post-transplant, as well as the number of hospitalization days post-transplant discharge. In SCD patients only, efficacy will also be measured based on the number of vaso-occlusive crises or acute chest syndrome events.

We also expect to initiate in mid-2013 a Phase I/II clinical study in the United States to evaluate our LentiGlobin product candidate in increasing hemoglobin production and eliminating or reducing transfusion dependence in patients with ß-thalassemia major, which we refer to as the HGB-204 Study. Up to 15 adults will be enrolled to evaluate production of hemoglobin containing $ß^{A-T87Q}$-globin for the six-month period between 18 and 24 months post-transplant, followed by long-term monitoring to assess safety and efficacy beyond the initial 24 months.

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Our strategic alliance with Celgene

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 will focus 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, 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. See Business Our strategic alliance with Celgene.

Our strategy

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 and orphan diseases. Central to this effort is a collective determination within our Company to provide these patients with hope for a better life in the face of limited or no long-term safe and effective treatment options. Specifically, our business strategy is based on the following principles:

- Relentlessly focus on serving our patients.
- Be the world s biggest gene therapy geeks, with world-class expertise in the field of gene therapy.
- Leverage our platform and technical expertise to build a gene therapy product engine for severe genetic and orphan diseases.
- Develop and commercialize drugs in our core disease areas and partner selectively to expand the scope of our pipeline.
- Pursue indications with high unmet medical need and greater probability of clinical, regulatory and commercial success.

Risks related to our business

Our ability to implement our business strategy is subject to numerous risks that you should be aware of before making an investment decision. These risks are described more fully in the section entitled Risk factors immediately following this prospectus summary. These risks include, among others:

- We have incurred significant losses since our inception, which we anticipate will continue for the foreseeable future. We have never generated revenue from product sales and may never be profitable.
- Failure to obtain additional funding when needed may force us to delay, limit or terminate our product development efforts or other operations.
- 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 for obtaining regulatory approval.

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

If our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

No gene therapy products have been approved in the United States and only one product has been approved in Europe.

Neither our current viral vectors nor our product candidates have ever been evaluated in human clinical studies, and we may experience unexpected results in the future.

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.

We expect to rely on third parties to conduct the majority of our current vector production, product manufacturing and clinical development. If they fail to meet deadlines or perform in an unsatisfactory manner our business could be harmed.

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.

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.

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

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 principal executive offices are located at 840 Memorial Drive, 4th Floor, Cambridge, MA 02139, and our telephone number is (617) 491-5601. Our website address is www.bluebirdbio.com. The information contained in, or that can be accessed through, our website is not part of this prospectus.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of this offering, (b) in which we have total annual gross revenue of at least $1.0 billion or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

We use Lenti-D and the bluebird bio logo as trademarks in the United States and other countries. We use and have registered LentiGlobin and bluebird bio in the United States.

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This prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork, and other visual displays, may appear without the ® or symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies. Except where the context requires otherwise, in this prospectus Company, bluebird, we, us and our refer to bluebird bio, Inc.

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The offering

Common stock offered by us	shares
Common stock to be outstanding after this offering	shares
Option to purchase additional shares	The underwriters have an option for a period of 30 days to purchase up to additional shares of our common stock.
Use of proceeds	We estimate that the net proceeds from this offering will be approximately $ million, or approximately $ million if the underwriters exercise their option to purchase additional shares in full, at an assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering to fund direct research and development expenses for our Phase II/III clinical study for our Lenti-D product candidate and our Phase I/II clinical studies for our LentiGlobin product candidate. We intend to use remaining amounts for general and administrative expenses (including personnel-related costs), potential future development programs, early-stage research and development, capital expenditures and working capital and other general corporate purposes. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary gene therapy businesses, technologies, products or assets. See Use of proceeds.
Risk factors	You should read the Risk factors section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Proposed Nasdaq Global Market symbol	BLUE

The number of shares of common stock to be outstanding after this offering is based on 6,599,419 shares of common stock outstanding as of March 31, 2013, which excludes 2,506,114 shares of unvested restricted stock subject to repurchase by us and 310,841,204 additional shares of our common stock issuable upon conversion of all of our outstanding shares of preferred stock upon closing of this offering.

The number of shares of our common stock to be outstanding after this offering excludes the following:

- 69,284,748 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2013 having a weighted-average exercise price of $0.19 per share;

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8,352,387 shares of common stock issuable upon the exercise of outstanding warrants as of March 31, 2013 having a weighted-average exercise price of $0.49 per share;

10,354,017 shares of common stock reserved for issuance pursuant to future equity awards under our 2010 Stock Option and Grant Plan, which will become available for issuance under our 2013 Stock Option and Incentive Plan immediately prior to this offering; and

shares of common stock reserved for issuance pursuant to future equity awards under our 2013 Stock Option and Incentive Plan, which will become effective immediately prior to this offering.

Except as otherwise indicated, all information contained in this prospectus:

reflects the conversion of all of our outstanding shares of preferred stock into an aggregate of 310,841,204 shares of common stock prior to the completion of this offering;

assumes the adoption of our amended and restated certificate of incorporation and amended and restated by-laws upon the completion of this offering;

assumes that the underwriters do not exercise their option to purchase additional shares;

assumes no exercise of outstanding options or warrants after March 31, 2013; and

reflects a one-for- reverse stock split of our common stock that will become effective prior to the effectiveness of the registration statement of which this prospectus forms a part.

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Summary consolidated financial data

The following summary consolidated financial data for the years ended December 31, 2012 and 2011 are derived from our audited consolidated financial statements appearing elsewhere in this prospectus. The summary consolidated financial data as of March 31, 2013 and for the three months ended March 31, 2012 and 2013 have been derived from our unaudited consolidated financial statements included elsewhere in this prospectus. In our opinion, these unaudited financial statements have been prepared on a basis consistent with our audited consolidated financial statements and contain all adjustments, consisting only of normal and recurring adjustments, necessary for a fair presentation of such consolidated financial data. You should read this data together with our audited consolidated financial statements and related notes appearing elsewhere in this prospectus and the information under the captions Selected consolidated financial data and Management s discussion and analysis of financial condition and results of operations. Our historical results are not necessarily indicative of our future results, and our operating results for the three-month period ended March 31, 2013 are not necessarily indicative of the results that may be expected for the fiscal year ending December 31, 2013 or any other interim periods or any future year or period.

(in thousands, except per share data)	Year ended December 31, 2011	Year ended December 31, 2012	Three months ended March 31, 2012	Three months ended March 31, 2013
			(unaudited)	
Consolidated statements of operations data:				
Revenue:				
Collaboration revenue	$	$	$	$ 1,042
Research and license fees	640	340	85	85
Grant revenue	242			
	882	340	85	1,127
Expenses:				
Research and development	11,409	17,210	3,858	5,284
General and administrative	4,615	6,846	1,363	2,324
Total expenses	16,024	24,056	5,221	7,608
Loss from operations	(15,142)	(23,716)	(5,136)	(6,481)
Other income (expense), net	(456)	46	68	(63)
Net loss	$ (15,598)	$ (23,670)	$ (5,068)	$ (6,544)
Net loss per share applicable to common stockholders basic and diluted(1)	$ (9.01)	$ (0.73)	$ (1.50)	$ (1.05)
Weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted	2,285	4,972	4,236	6,226
Pro forma net loss per share applicable to common stockholders basic and diluted (unaudited)(1)		$ (0.10)		$ (0.02)
Pro forma weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted (unaudited)		248,700		317,067

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(in thousands)	Actual	As of March 31, 2013 Pro Forma(2) (unaudited)	Pro Forma Adjusted (3)(4)
Consolidated balance sheet data:			
Cash and cash equivalents	$ 131,836	$ 131,836	
Working capital	105,390	105,390	
Total assets	137,459	137,459	
Preferred stock	122,177		
Common stock and additional paid-in capital	15,966	138,399	
Total stockholders (deficit) equity	(61,595)	58,501	

(1) See Notes 2 and 15 within the notes to our consolidated financial statements appearing elsewhere in this prospectus for a description of the method used to calculate basic and diluted net loss per share of common stock and pro forma basic and diluted net loss per share of common stock.

(2) Pro forma to reflect the conversion of all outstanding shares of our preferred stock into shares of our common stock, and the reclassification of our outstanding warrants to purchase our Series B preferred stock to our common stock, upon the closing of this offering.

(3) Pro forma as adjusted to further reflect the sale of shares of our common stock offered in this offering, assuming an initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

(4) A $1.00 increase (decrease) in the assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash and cash equivalents and total stockholders (deficit) equity by approximately $ million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. A share increase in the number of shares offered by us together with a concomitant $1.00 increase in the assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, would increase each of cash and cash equivalents and total stockholders (deficit) equity by approximately $ million after deducting underwriting discounts and commissions and any estimated offering expenses payable by us. Conversely, a share decrease in the number of shares offered by us together with a concomitant $1.00 decrease in the assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, would decrease each of cash and cash equivalents and total stockholders (deficit) equity by approximately $ million after deducting underwriting discounts and commissions and any estimated offering expenses payable by us.

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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 prospectus, including our financial statements and related notes thereto, 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 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 $15.6 million and $23.7 million for the years ended December 31, 2011 and 2012, respectively, and $6.5 million for the three months ended March 31, 2013. As of March 31, 2013, we had an accumulated deficit of $79.9 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 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 Corporation;
- 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;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;

seek to identify and validate additional product candidates;

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- acquire or in-license other product candidates and technologies;
- make milestone or other payments under any in-license agreements;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel;
- create 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 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, scalable, 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 market acceptance of our product candidates and gene therapy as a viable treatment option;
- addressing any competing technological and market developments;

implementing additional internal systems and infrastructure, as needed;

identifying and validating new gene therapy product candidates;

negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;

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maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and

attracting, hiring and retaining qualified personnel.

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.

Even if this offering is successful, 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 March 31, 2013, our cash and cash equivalents were $131.8 million. We estimate that the net proceeds from this offering will be approximately $ million, assuming an initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting estimated underwriting discounts and commissions and offering expenses payable by us. We expect that the net proceeds from this offering and our existing cash and cash equivalents will be sufficient to fund our current operations through at least the end of 2015. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. Raising funds in the current economic environment may present additional challenges. 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 considerations.

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

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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 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 Europe.

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 scalable 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 from the EMA 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 either Europe or the United States. Approvals by the EMA may not be indicative of what the FDA may require for approval.

Regulatory requirements governing gene and cell therapy products have changed frequently 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

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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, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other regulatory bodies to change the requirements for approval of any of our product candidates.

These regulatory review committees and advisory groups and the new 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 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.

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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. The total annual incidence of ß-thalassemia is estimated at one in 100,000 throughout the world and one in 10,000 in the European Union, and 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 incidence rate for adrenoleukodystrophy, or ALD, the superset of CCALD, is approximately one in 20,000 newborn males, and the U.S. National Institute of Health, or NIH, estimates a prevalence of one in 20,000. 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. We plan to seek initial marketing approval in the United States and Europe. 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 and 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 reaching agreement on acceptable terms with prospective CROs and clinical study sites;

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- delays in obtaining required Institutional Review Board, or IRB, 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;
- 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 guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- 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 bridge 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 marketing 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 subject to changes with the way the product is administered;

be required to perform additional clinical studies 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 distribution in the form of a modified risk evaluation and mitigation strategy;

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be subject to the addition of labeling statements, such as warnings or contraindications;

be sued; or

experience damage to our reputation.

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

Neither our current viral vectors nor our product candidates have ever been evaluated in human clinical studies, 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.

The results from our ALD-102 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 conduct additional clinical studies, or evaluate subjects for an additional follow-up period.

The FDA has advised us that our ALD-102 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

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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 ALD-102 Study, the FDA may require us to conduct a second clinical study, possibly involving a larger sample size or a different clinical study design, particularly if the FDA does not find the results from the ALD-102 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 ALD-102 Study was not designed to achieve a statistically significant efficacy determination. Rather, we expect that safety and efficacy will be evaluated in light of the data collected in our retrospective data collection study, the ALD-101 Study. However, due to the nature of this retrospective data collection 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 ALD-102 Study. Thus, we expect that the FDA will assess the totality of the safety and efficacy data from our ALD-102 Study 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 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 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 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. In published studies, lentiviral vectors have demonstrated an improved safety profile over gamma-retroviral vectors, with no known 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 five 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.

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 planned or future 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 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 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 FDA

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typically advises that patients treated with gene therapy undergo follow-up observations for potential adverse events for a 15-year period. 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 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, product manufacturing, protocol development, 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, protocol development, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to these items.

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. 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.

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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 submissions and approval of our product candidates.

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;
- 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. 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 on a timely basis and must adhere to the FDA s good laboratory practices, or GLP, and GMP regulations enforced by the FDA through its facilities inspection program. Some of our contract manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA 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

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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 approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those 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 can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or 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. An alternative manufacturer would need to be qualified through a BLA supplement 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 IND-enabling studies and 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

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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 effectiveness 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.

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. 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

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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 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 scalable manufacturing process for LentiGlobin, which we plan 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 academic institutions and one third-party contract manufacturer in the United States and Europe, respectively, 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 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

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the necessary quantities of viral vectors and our product candidates, or in compliance with GMP, or in compliance with 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, which is a rapidly changing field. 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, Sangamo BioSciences Inc., HemaQuest Pharmaceuticals, Inc., Merck & Co., Inc., Novartis AG and GlycoMimetics Inc. 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

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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 ten 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

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part on the medical community, patients, and third-party 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;
- 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;
- unexpected changes in tariffs, trade barriers and regulatory requirements;

economic weakness, including inflation, or political instability in particular foreign economies and markets;

compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;

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- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;

- workforce uncertainty in countries where labor unrest is more common than in the United States;

- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

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. 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. 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

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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 of which 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 orphan 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

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

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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 and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team and key employees listed under Management located elsewhere in this prospectus, 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 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 or key employee 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 March 31, 2013, we had 50 full-time employees. As we mature and undertake 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. For example, in the past there have been errors in the preparation of our financial statements and there can be no assurance that other errors will not occur in the future as we grow. 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

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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 future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

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. 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 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;

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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 of $5,000,000 per occurrence and $5,000,000 aggregate limit. 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

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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 platform. 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 will incur significant increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

As a public company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, as well as rules subsequently implemented by the Securities and Exchange Commission, or SEC, and The Nasdaq Global 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. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as say on pay and proxy access. Recent legislation permits smaller emerging growth companies to implement many of these requirements over a longer period and up to five years from the pricing of this offering. We intend to take advantage of this new

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legislation but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. 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. We estimate that we will annually incur approximately $1.0 million to $3.0 million in additional expenses to comply with the requirements imposed on us as a public company.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the recent global financial crisis, could result in a variety of risks to our business, including, weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. This is particularly true in Europe, which is undergoing a continued severe economic crisis. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

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

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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.

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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.

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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.

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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. See Business License agreements for a description of our license agreements with Inserm-Transfert, Institut Pasteur, Stanford University, the Massachusetts Institute of Technology and Research Development Foundation, which includes a description of the termination provisions of these agreements.

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.

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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.

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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.

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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 have not yet registered trademarks for a commercial trade name for Lenti-D and failure to secure such registrations could adversely affect our business.

We have not yet registered trademarks for a commercial trade name for Lenti-D. During trademark registration proceedings, we may receive rejections. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the U.S. PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Moreover, any name we

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propose to use with our product candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

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 this offering and 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 initial public offering price.

Prior to this offering, there has not been a public market for our common stock. An active trading market for our common stock may not develop following this offering. You may not be able to sell your shares quickly or at the market price if trading in our common stock is not active. The initial public offering price for the shares will be determined by negotiations between us and the representative of the underwriters and may not be indicative of prices that will prevail in the trading market.

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The market price of our common stock is likely to 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.

In addition, companies trading in the stock market in general, and The Nasdaq Global 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.

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Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Our executive officers, directors, five percent stockholders and their affiliates beneficially own approximately % of our voting stock and, upon closing of this offering, that same group will beneficially own approximately % of our outstanding voting stock. Therefore, even after this offering, these stockholders will have the ability to influence us through their ownership positions. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

We are an emerging growth company, and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or, if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time, we would cease to be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

Investors purchasing shares of common stock in this offering will pay a price per share that substantially exceeds the pro forma book value per share of our tangible assets after subtracting our liabilities. As a result, investors purchasing shares of common stock in this offering will incur immediate dilution of $ per share, based on an assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, and our pro forma net tangible book value as of March 31, 2013. Further, based on these assumptions, investors purchasing shares of common stock in this offering will contribute approximately % of the total amount invested by stockholders since our inception, but will own only approximately % of the shares of common stock outstanding. For information on how the foregoing amounts were calculated, see Dilution.

This dilution is due to the substantially lower price paid by our investors who purchased shares prior to this offering as compared to the price offered to the public in this offering, and the exercise of stock options granted to our employees. In addition, as of March 31, 2013, options to purchase 69,284,748 shares of our common stock at a weighted average exercise price of $0.19 per share were outstanding. The exercise of any of these options would result in additional dilution. As a result of the dilution to investors purchasing shares in this offering, investors may receive significantly less than the purchase price paid in this offering, if anything, in the event of our liquidation.

Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market after the lock-up and other legal restrictions on resale discussed in this prospectus lapse, the market price of our common stock could decline. Based upon the number of shares of common stock, on an as-converted basis, outstanding as of , 2013, upon the closing of this offering, we will have outstanding a total of shares of common stock, assuming no exercise of the underwriters option to purchase additional shares. Of these shares, approximately shares of our common stock, plus any shares sold upon exercise of the underwriters option to purchase additional shares, will be freely tradable, without restriction, in the public market immediately following this offering, assuming that current stockholders do not purchase shares in this offering. J.P. Morgan Securities LLC and Merrill Lynch, Pierce, Fenner & Smith Incorporated, however, may, in their sole discretion, permit our officers, directors and other stockholders who are subject to these lock-up agreements to sell shares prior to the expiration of the lock-up agreements.

The lock-up agreements pertaining to this offering will expire 180 days from the date of this prospectus (subject to extension upon the occurrence of specified events). After the lock-up agreements expire, as of , 2013, up to an additional shares of common stock will be eligible for sale in the public market, of which shares are held by directors, executive officers and other affiliates and will be subject to Rule 144 under the Securities Act of 1933, as amended, or the Securities Act.

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In addition, as of , 2013, shares of common stock that are either subject to outstanding options, reserved for future issuance under our equity incentive plans or subject to outstanding warrants will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules, the lock-up agreements and Rule 144 and Rule 701 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the market price of our common stock could decline.

After this offering, the holders of approximately million shares of our common stock, or approximately % of our total outstanding common stock as of , 2013, will be entitled to rights with respect to the registration of their shares under the Securities Act, subject to the lock-up agreements described above. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the market price of our common stock.

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 will automatically increase each year by up to % 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 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 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 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.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled Use of proceeds,

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and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest the net proceeds from this offering in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders.

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 believe we may have triggered an ownership change limitation. 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, which will become effective upon the closing of this offering, 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;

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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, effective upon completion of this offering, 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

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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.

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Cautionary note regarding forward-looking statements

This prospectus contains forward-looking statements that involve risks and uncertainties. All statements other than statements of historical facts contained in this prospectus 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, see 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 the caption Risk factors.

Any forward-looking statements in this prospectus 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 Risk factors and elsewhere in this prospectus. 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.

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This prospectus 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.

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Use of proceeds

We estimate that the net proceeds from the sale of shares of common stock in this offering will be approximately $ million at an assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds will be approximately $ million after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Each $1.00 increase or decrease in the assumed initial public offering price of $ per share would increase or decrease our net proceeds by $ million, assuming the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We are undertaking this offering in order to access the public capital markets and to increase our liquidity. We intend to use the net proceeds of this offering as follows:

- Approximately $ million to fund direct research and development expenses for our ALD-102 Study, a Phase II/III clinical study of Lenti-D to evaluate its safety and efficacy in subjects with childhood cerebral adrenoleukodystrophy;

- Approximately $ million to fund direct research and development expenses for our HGB-204 Study, a Phase I/II clinical study in the United States of LentiGlobin to evaluate its safety and efficacy in subjects with ß-thalassemia major;

- Approximately $ million to fund direct research and development expenses for our HGB-205 Study, a Phase I/II clinical study in Europe of LentiGlobin to evaluate its safety and efficacy in subjects with ß-thalassemia major and sickle cell disease; and

- The remainder for general and administrative expenses (including personnel-related costs), potential future development programs, early-stage research and development, capital expenditures and working capital and other general corporate purposes.

Our expected use of net proceeds from this offering represents our current intentions based upon our present plans and business condition. As of the date of this prospectus, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering or the amounts that we will actually spend on the uses set forth above. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary gene therapy businesses, technologies, products or assets. Due to the many variables inherent to the development of gene therapy products at this time, such as the timing of patient enrollment and evolving regulatory requirements, we cannot currently predict the stage of development we expect the net proceeds of this offering to achieve for our clinical studies and product candidates.

The amount and timing of our actual expenditures will depend upon numerous factors, including the results of our research and development efforts, the timing and success of preclinical studies, our ongoing clinical studies or clinical studies we may commence in the future and the timing of regulatory submissions. As a result, our management will have broad discretion over the use of the net proceeds from this offering.

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Pending the use of the proceeds from this offering, we intend to invest the net proceeds in short-term, interest-bearing, investment-grade securities, certificates of deposit or government securities.

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Dividend policy

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors.

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Capitalization

The following table sets forth our cash, cash equivalents and capitalization as of March 31, 2013:

- on an actual basis;
- on a pro forma basis to reflect conversion of all outstanding shares of our preferred stock into an aggregate of 310,841,204 shares of common stock and the reclassification of our outstanding warrants to purchase shares of preferred stock to common stock, in each case prior to the completion of this offering; and
- on a pro forma as adjusted basis to additionally reflect the issuance and sale by us of shares of our common stock in this offering, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, at an assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus.

You should read this information together with our audited financial statements and related notes appearing elsewhere in this prospectus and the information set forth under the heading Selected consolidated financial data and Management s discussion and analysis of financial condition and results of operations.

	As of March 31, 2013		
(in thousands, except per share data)	**Actual**	**Pro forma**	**Pro forma as adjusted**
		(unaudited)	
Cash and cash equivalents	$ 131,836	$ 131,836	
Preferred stock warrant liability	256		
Series A-2 convertible preferred stock, $0.01 par value: 22,304 shares authorized; 22,304 shares issued and outstanding at March 31, 2013, and no shares issued and outstanding pro forma and pro forma as adjusted	7,137		
Series B convertible preferred stock, $0.01 par value: 115,779 shares authorized; 115,204 shares issued and outstanding at March 31, 2013, and no shares issued and outstanding pro forma and pro forma as adjusted	40,321		
Series C convertible preferred stock, $0.01 par value: 39,943 shares authorized; 39,943 shares issued and outstanding at March 31, 2013, and no shares issued and outstanding pro forma and pro forma as adjusted	12,382		
Series D convertible preferred stock, $0.01 par value: 120,409 shares authorized; 120,409 shares issued and outstanding at March 31, 2013, and no shares issued and outstanding pro forma and pro forma as adjusted	60,000		
Stockholders deficit:			
Series A-1 convertible preferred stock, $0.01 par value: 18,817 shares authorized; 12,981 shares issued and outstanding at March 31, 2013, and no shares issued and outstanding pro forma and pro forma as adjusted	2,337		
Common stock, $0.01 par value; 408,000 shares authorized, actual and pro forma; 6,599 shares issued and outstanding at March 31, 2013, and 317,440 shares issued and outstanding pro forma(1); shares authorized and shares issued and outstanding, pro forma as adjusted	66	3,174	
Additional paid-in capital	15,900	135,225	
Accumulated deficit	(79,898)	(79,898)	
Total stockholders (deficit) equity	(61,595)	58,501	
Total capitalization	$ 58,501	$ 58,501	

(1) Excludes 2,506 shares of unvested restricted common stock.

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The actual, pro forma and pro forma as adjusted outstanding shares information in the table above excludes the following:

- 69,284,748 shares of common stock issuable upon the exercise of outstanding stock options having a weighted-average exercise price of $0.19 per share;
- 8,352,387 shares of common stock issuable upon the exercise of outstanding warrants having a weighted-average exercise price of $0.49 per share;
- 10,354,017 shares of common stock reserved for issuance pursuant to future equity awards under our 2010 Stock Option and Grant Plan; and
- shares of common stock reserved for issuance pursuant to future equity awards under our 2013 Stock Option and Incentive Plan.

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Dilution

If you invest in our common stock in this offering, your interest will be diluted to the extent of the difference between the initial public offering price per share of our common stock in this offering and the pro forma as adjusted net tangible book value per share of our common stock after this offering.

As of March 31, 2013, we had pro forma net tangible book value of $58.5 million, or $0.18 per share of common stock, taking into account the expected conversion of our outstanding preferred stock into common stock and reclassification of our outstanding warrants to purchase our Series B preferred stock into common stock, prior to the completion of this offering. Without giving effect to the conversion of our outstanding preferred stock into common stock, we had a historical net tangible book value of $(61.6) million, or $(9.33) per share of common stock, as of March 31, 2013. Historical net tangible book value per share is equal to our total tangible assets, less total liabilities and preferred stock, divided by the number of outstanding shares of our common stock (excluding 2,506,114 shares of unvested restricted stock subject to repurchase by us). After giving effect to (1) the conversion of all of our preferred stock into 310,841,204 shares of common stock prior to the completion of this offering and (2) the sale of shares of common stock in this offering, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, at an assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, our pro forma as adjusted net tangible book value as of March 31, 2013 would have been approximately $ million, or approximately $ per share of common stock. This represents an immediate increase in pro forma as adjusted net tangible book value of $ per share to our existing stockholders and an immediate dilution of $ per share to investors participating in this offering. The following table illustrates this per share dilution:

Assumed initial public offering price per share		$
Historical net tangible book value per share as of March 31, 2013	$ (9.33)	
Increase attributable to the conversion of outstanding preferred stock and reclassification of preferred stock warrants		
Pro forma net tangible book value per share as of March 31, 2013		
Increase in net tangible book value per share attributable to new investors		
Pro forma net tangible book value per share after this offering		
Dilution per share to new investors		$

Each $1.00 increase (decrease) in the assumed initial public offering price of $ per share would increase (decrease) our pro forma as adjusted net tangible book value by approximately $ million, the pro forma as adjusted net tangible book value per share by approximately $ per share and the dilution to investors purchasing shares in this offering by approximately $ per share, assuming the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

The following table summarizes, on a pro forma as adjusted basis as of March 31, 2013, the differences between the number of shares of common stock purchased from us, the total consideration and the average price per share paid by existing stockholders (giving effect to the conversion of all of our preferred stock into 310,841,204 shares of common stock prior to the

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completion of this offering) and by investors participating in this offering, after deducting estimated underwriting discounts and commissions and estimated offering expenses, at an assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus.

	Shares purchased		Total consideration		Average price per share
	Number	Percent	Amount	Percent	
Existing stockholders	319,946,737	%	$	%	$
New investors		%		%	$
Total		100%	$	%	

The number of shares of common stock to be outstanding after this offering is based on the number of shares outstanding as of March 31, 2013 and excludes the following:

- 69,284,748 shares of common stock issuable upon the exercise of outstanding stock options having a weighted-average exercise price of $0.19 per share;
- 8,352,387 shares of common stock issuable upon the exercise of outstanding warrants having a weighted-average exercise price of $0.49 per share;
- 10,345,017 shares of common stock reserved for issuance pursuant to future equity awards under our 2010 Stock Option and Grant Plan; and
- shares of common stock reserved for issuance pursuant to future equity awards under our 2013 Stock Option and Incentive Plan.

If the underwriters exercise their option to purchase additional shares in full, pro forma as adjusted net tangible book value as of , 2013 will increase to $ million, or $ per share, representing an increase to existing stockholders of $ per share, and there will be an immediate dilution of an additional $ per share to new investors.

Furthermore, we may choose to raise additional capital through the sale of equity or convertible debt securities due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. New investors will experience further dilution if any of our outstanding options or warrants are exercised, new options are issued and exercised under our equity incentive plans or we issue additional shares of common stock, other equity securities or convertible debt securities in the future.

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Selected consolidated financial data

The selected consolidated statements of operations data and the consolidated balance sheet data are derived from our audited consolidated financial statements appearing elsewhere in this prospectus. The selected consolidated financial data as of March 31, 2013 and for the three months ended March 31, 2013 and 2012 have been derived from our unaudited consolidated financial statements included elsewhere in this prospectus. In our opinion, these unaudited financial statements have been prepared on a basis consistent with our audited consolidated financial statements and contain all adjustments, consisting only of normal and recurring adjustments, necessary for a fair presentation of such consolidated financial data. You should read this data together with our audited consolidated financial statements and related notes appearing elsewhere in this prospectus and the information under the caption Management s discussion and analysis of financial condition and results of operations. Our historical results are not necessarily indicative of our future results, and our operating results for the three-month period ended March 31, 2013 are not necessarily indicative of the results that may be expected for the fiscal year ending December 31, 2013 or any other interim periods or any future year or period.

(in thousands, except per share data)	Year ended December 31, 2011	2012	Three months ended March 31, 2012	2013
			(unaudited)	
Consolidated statements of operations data:				
Revenue:				
Collaboration revenue	$	$	$	$ 1,042
Research and license fees	640	340	85	85
Grant revenue	242			
	882	340	85	1,127
Expenses:				
Research and development	11,409	17,210	3,858	5,284
General and administrative	4,615	6,846	1,363	2,324
Total expenses	16,024	24,056	5,221	7,608
Loss from operations	(15,142)	(23,716)	(5,136)	(6,481)
Other income (expense), net	(456)	46	68	(63)
Net loss	$ (15,598)	$ (23,670)	$ (5,068)	$ (6,544)
Net loss per share applicable to common stockholders basic and diluted(1)	$ (9.01)	$ (0.73)	$ (1.50)	$ (1.05)
Weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted	2,285	4,972	4,236	6,226
Pro forma net loss per share applicable to common stockholders basic and diluted (unaudited)(1)		$ (0.10)		$ (0.02)
Pro forma weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted (unaudited)		248,700		317,067

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(in thousands)	Actual	As of March 31, 2013 Pro Forma Pro Forma(2) (unaudited)	Adjusted (3)(4)
Consolidated balance sheet data:			
Cash and cash equivalents	$ 131,836	$ 131,836	
Working capital	105,390	105,390	
Total assets	137,459	137,459	
Preferred stock	122,177		
Common stock and additional paid-in capital	15,966	138,399	
Total stockholders (deficit) equity	(61,595)	58,501	

(1) See Notes 2 and 15 within the notes to our consolidated financial statements appearing elsewhere in this prospectus for a description of the method used to calculate basic and diluted net loss per common share and pro forma basic and diluted net loss per common share.

(2) Pro forma to reflect the conversion of all outstanding shares of our preferred stock into shares of common stock, and the reclassification of our outstanding warrants to purchase our Series B preferred stock to our common stock, upon the closing of this offering.

(3) Pro forma as adjusted to further reflect the sale of shares of our common stock offered in this offering, assuming an initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

(4) A $1.00 increase (decrease) in the assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash and cash equivalents and total stockholders (deficit) equity by approximately $ million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. A share increase in the number of shares offered by us together with a concomitant $1.00 increase in the assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, would increase each of cash and cash equivalents and total stockholders (deficit) equity by approximately $ million after deducting underwriting discounts and commissions and any estimated offering expenses payable by us. Conversely, a share decrease in the number of shares offered by us together with a concomitant $1.00 decrease in the assumed initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus, would decrease each of cash and cash equivalents and total stockholders (deficit) equity by approximately $ million after deducting underwriting discounts and commissions and any estimated offering expenses payable by us.

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Management s discussion and analysis of financial condition and results of operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing in this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the Risk factors section of this prospectus, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biotechnology company focused on transforming the lives of patients with severe genetic and orphan diseases using gene therapy. 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*. We and our scientific collaborators have generated what we believe is human proof-of-concept data for our gene therapy platform in two underserved diseases, each of which has been granted orphan drug status by U.S. and European regulatory authorities. We expect to initiate in late 2013 a Phase II/III clinical 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. We also expect to initiate in mid-2013 Phase I/II clinical studies in the United States and Europe of our next most advanced product candidate, LentiGlobin, to evaluate its safety and efficacy in subjects with ß-thalassemia major and, in the European clinical study, sickle cell disease, or SCD, which are rare, hereditary blood disorders that often lead to severe anemia and shortened lifespans. In addition, in March 2013, we announced a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel, disease-altering gene therapies in oncology.

Since our inception in 1992, we have devoted substantially all of our resources to our development efforts relating to our product candidates, including activities to manufacture product in compliance with good manufacturing practices, or GMP, preparing to conduct clinical studies of our product candidates, providing general and administrative support for these operations and protecting our intellectual property. We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations primarily through the private placement of preferred stock, common stock, convertible notes and warrants to purchase common stock. In addition, in October 2012, we were awarded a $9.3 million grant from the California Institute for Regenerative Medicine, or CIRM, to fund our U.S. ß-thalassemia program. This grant will be issued in quarterly installments and is expected to be utilized over a four-year period starting in the second quarter of 2013.

In March 2013, we entered into a strategic collaboration with Celgene Corporation, or Celgene, to discover, develop and commercialize novel, disease-altering gene therapies in oncology. This collaboration has an initial term of three years, and Celgene has made a $75 million up-front, non-refundable cash payment to us as consideration for entering into the

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collaboration. During the three months ended March 31, 2013, we recognized $1.0 million of revenue associated with our collaboration with Celgene related to the research and development services performed. As of March 31, 2013, there is $74.0 million of deferred revenue related to our collaboration with Celgene that is classified as current or long-term in the accompanying balance sheet based on the contractual term of the arrangement.

We have never been profitable and have incurred net losses in each year since inception. Our net losses were $15.6 million and $23.7 million for the years ended December 31, 2011 and 2012, and $5.1 million and $6.5 million for the three months ended March 31, 2012 and 2013, respectively. 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 activities, as we:

- conduct clinical studies for our Lenti-D and LentiGlobin product candidates;
- continue our research and development efforts;
- increase research and development related activities for the discovery and development of oncology product candidates in connection with our recently-announced strategic collaboration with Celgene;
- 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 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.

Financial operations overview

Revenue

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

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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.

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.

Grant revenue is primarily generated through research and development grant programs offered by federal, state, and local governments. Revenue is recognized when there is reasonable assurance that the grant will be received and we have complied with the terms of the grant.

Our ability to generate product revenue and become profitable depends upon our ability to successfully commercialize products. We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates and begin to commercialize any approved 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.

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 investigative sites that will conduct our clinical studies;
- the cost 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; and
- costs associated with preclinical activities and regulatory operations.

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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;
- future clinical study results;
- uncertainties in clinical study enrollment rate;
- significant and changing government regulation; 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.

From inception through March 31, 2013, we have incurred $69.8 million in research and development expenses. We plan to increase our research and development expenses for the foreseeable future as we continue the development of our Lenti-D and LentiGlobin product candidates and conduct research and development activities under our recently-announced strategic collaboration with Celgene. Our current planned research and development activities include the following:

- We plan to initiate during late 2013 a Phase II/III clinical study to examine the feasibility, safety and efficacy of our Lenti-D product candidate.
- We plan to initiate during mid-2013 a Phase I/II clinical study in France to study the feasibility, safety and efficacy of our LentiGlobin product candidate in subjects with ß-thalassemia major and SCD.
- We plan to initiate during mid-2013 a Phase I/II clinical study in the United States to study the feasibility, safety and efficacy of our LentiGlobin product candidate in subjects with ß-thalassemia major.
- 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 startup 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. We

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do not allocate personnel-related costs, costs associated with our general platform improvements, depreciation or other indirect costs to specific programs, as they are deployed across multiple projects under development and, as such, are separately classified as personnel and other expenses in the table below:

(in thousands)	Year ended December 31, 2011	2012	Three months ended March 31, 2012	2013
			(unaudited)	
Lenti-D	$ 2,900	$ 3,966	$ 1,100	$ 1,076
LentiGlobin	1,416	5,259	551	1,362
Total direct research and development expenses	4,316	9,225	1,651	2,438
Employee and contractor-related expenses	5,090	6,150	1,686	2,055
Platform-related lab expenses	717	727	265	348
Facility expenses	619	709	187	295
Other expenses	667	399	69	148
Personnel and other expenses	7,093	7,985	2,207	2,846
Total research and development expenses	**$ 11,409**	**$ 17,210**	**$ 3,858**	**$ 5,284**

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 and human resource functions. Other general and administrative expenses include facility-related costs and professional fees for directors, accounting and legal services 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 Securities and Exchange Commission 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 cash and cash equivalents and the re-measurement gain or loss associated with the change in the fair value of the preferred stock warrant liability.

We use the Black-Scholes option pricing model to estimate the fair value of the warrants. We base 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

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preferred stock underlying the warrants. The re-measurement gain or loss associated with the change in the fair value of the preferred stock warrant liability each reporting period is recognized as a component of other income (expense), net.

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 U.S. 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 expenses and stock-based compensation. 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.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this prospectus, 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 the 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 March 31, 2013, 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

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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

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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.

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.

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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. 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. We recognize the compensation cost of stock-based awards to employees on a straight-line basis over the vesting period of the award and using an accelerated attribution model for awards to non-employees. Described below is the methodology we have utilized in measuring stock-based compensation expense. Following the consummation of this offering, stock option and restricted stock values will be 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 (a) the expected volatility of our stock, (b) the expected term of the award, (c) the risk-free interest rate, and (d) 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 have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. For these analyses, we have selected 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 have estimated 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 are 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.

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

	Year ended December 31,		Three months ended March 31,	
	2011	2012	2012	2013
			(unaudited)	
Expected volatility	83.0%	79.6%	78.8%	82.0%
Expected term (in years)	6.1	6.1	6.1	6.1
Risk-free interest rate	1.7%	1.0%	1.1%	1.0%
Expected dividend yield	0.0%	0.0%	0.0%	0.0%

The following table presents the grant dates, number of underlying shares and related exercise prices or purchase prices of stock options granted and restricted stock awards, or RSAs, issued between January 1, 2011 and March 31, 2013, along with the corresponding exercise price for each option grant and the fair value per share utilized to calculate stock-based compensation expense:

Date of grant	Type of award	Number of shares	Exercise price (options) or purchase price (restricted stock) per share	Common stock fair value per share on grant date
7/13/2011	Option	11,818,294	$ 0.11	$ 0.11
7/13/2011	Restricted stock award	272,941	0.11	0.11
10/25/2011	Option	5,920,069	0.11	0.11
1/8/2012	Option	3,591,408	0.11	0.11
2/10/2012	Option	1,236,182	0.11	0.11
4/13/2012	Option	2,982,369	0.11	0.11
6/4/2012	Option	4,045,000	0.11	0.11
10/9/2012	Option	3,044,000	0.14	0.14
1/16/2013	Option	26,554,400	0.29	0.29
2/4/2013	Option	1,290,000	0.29	0.29

Stock-based compensation totaled approximately $0.8 million for the year ended December 31, 2012 and $0.7 million for the three months ended March 31, 2013. As of March 31, 2013, we had $6.5 million of total unrecognized compensation expense, net of related forfeiture estimates, which is expected to be recognized over a weighted-average remaining vesting period of approximately 3.6 years. We expect the impact of our stock-based compensation expense for stock options and restricted stock granted to employees and non-employees to grow in future periods due to the potential increases in the value of our common stock and headcount.

Fair value of stock options

We have historically granted stock options at exercise prices not less than the fair value of our common stock. As there has been no public market for our common stock to date, the estimated fair value of our common stock has been determined contemporaneously by our board of directors based on valuation estimates provided by management and prepared in accordance with the framework of the American Institute of Certified Public Accountants Technical Practice Aid, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*, or AICPA Practice Aid, as well as independent third-party valuations. Our contemporaneous valuations of

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our common stock as of April 21, 2011, April 15, 2012, July 23, 2012, December 31, 2012 and March 31, 2013 were based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector and the prices at which we sold shares of preferred stock, the superior rights and preferences of securities senior to our common stock at the time of each grant and the likelihood of achieving a liquidity event such as an initial public offering.

April 21, 2011 valuation

For the contemporaneous valuation at April 21, 2011, we used the back-solve method of the option-pricing method, or OPM, which derives the implied equity value for one type of equity security from a contemporaneous transaction involving another type of equity security. We applied the OPM back-solve method to solve for the equity value and corresponding value of common stock based on the $0.37554 per share price for the sale of Series C preferred stock in April 2011, which was led by an unrelated investor that had not previously invested in our Company. Given the proximity to the initial Series C preferred stock financing, we believe the per share issuance price of the Series C preferred stock provides an indication of the fair value of our equity as of April 21, 2011.

The OPM treats common stock and preferred stock as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company s securities changes. Under this method, the common stock has value only if the funds available for distribution to stockholders exceed the value of the liquidation preference at the time of a liquidity event, such as a strategic sale, merger or initial public offering, or IPO, assuming the enterprise has funds available to make a liquidation preference meaningful and collectible by the holders of preferred stock. The common stock is modeled as a call option on the underlying equity value at a predetermined exercise price. In the model, the exercise price is based on a comparison with the total equity value rather than, as in the case of a regular call option, a comparison with a per share stock price. Thus, common stock is considered to be a call option with a claim on the enterprise at an exercise price equal to the remaining value immediately after the preferred stock is liquidated. The option-pricing method uses the Black-Scholes option pricing model to price the call options. This model defines the securities fair values as functions of the current fair value of a company and uses assumptions such as the anticipated timing of a potential liquidity event and the estimated volatility of the equity securities.

We estimated the time to liquidity as 3.3 years based on then-current plans and estimates of our board of directors and management regarding a liquidity event. The risk free rate was estimated as the interpolated 3.3 year yield on government bonds.

We applied a discount for lack of marketability to the value indicated for our common stock. A discount is appropriate because our common stock is unregistered, and the holder of a minority interest in the common stock may not influence the timing of a liquidity event for our Company. Our estimate of the appropriate discount for lack of marketability took into consideration put option methodologies consistent with the AICPA Practice Aid. A put option model indicated a discount of 47%. We selected a smaller discount after taking into account empirical studies of restricted stock issued by publicly-traded companies.

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The following table summarizes the significant assumptions used to determine the fair value of our common stock of $0.11 as of April 21, 2011:

April 21, 2011 valuation

Key assumptions	
Liquidity date	8/8/2014
Annual volatility	75%
Risk-free interest rate	1.3%
Discount for lack of marketability (DLOM)	35%
Estimated per share present value of marketable common stock (before DLOM)	$ 0.17

April 15, 2012 valuation

For the contemporaneous valuation at April 15, 2012, we used the guideline public company, or GPC, method under the market approach to value our equity. We identified two categories of GPCs. The first category consists of GPCs which are comparable to our Company in certain respects, such as a focus on gene therapy, dependence on a relatively limited number of compounds and exposure to risks associated with clinical studies. Similar to our Company, the majority of the GPCs have more than one product in various stages of development. The companies in this category are AVI BioPharma, CytRx Corporation, Oxford BioMedica, Sangamo Biosciences, and Synageva BioPharma. We considered the average enterprise values of these companies as one indication of the value of our equity. The second category consists of GPCs in the drug development industry which have completed IPOs within the year preceding the April 15, 2012 appraisal date. These companies differ in therapy focus but are similar to our Company in that they depend on a relatively limited number of compounds and are subject to risks associated with clinical studies. As an indicator of value, we considered the increase in value, or step-up, from the most-recent preferred round to the IPO price for each of these GPCs. We considered the median step-up as one indication of value for our equity. The values indicated by these two categories of GPCs were similar, and we assumed an average of the two values.

For the valuation at April 15, 2012, we used the OPM to allocate equity value among our preferred and common securities. Significant assumptions for the OPM included volatility, the risk-free rate, and the time to liquidity. We calculated annual rates of volatility based on weekly historical trading data for a group of guideline public companies. The estimated time to liquidity was based on a 45% probability of liquidity in 2.72 years, a 45% probability of liquidity in 3.72 years and a 10% probability of liquidity in 1.46 years. The anticipated timing and probability of a liquidity event was based on then-current plans and estimates of our board of directors and management. The weighted-average time to liquidity was 3.04 years. We used the yield on three-year U.S. Treasuries as a risk-free rate.

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We applied a discount for lack of marketability to the value indicated for our common stock. A discount is appropriate because our common stock is unregistered, and the holder of a minority interest in the common stock may not influence the timing of a liquidity event for our Company. Our estimate of the appropriate discount for lack of marketability took into consideration put option methodologies consistent with the AICPA Practice Aid. Put option models indicated discounts of 30 to 68%. We selected a smaller discount after taking into account empirical studies of restricted stock issued by publicly-traded companies. The following table summarizes the significant assumptions used to determine the fair value of our common stock of $0.11 as of April 15, 2012:

April 15, 2012 valuation

Key assumptions	
Liquidity date	7/5/2015
Annual volatility	72%
Risk-free interest rate	0.4%
Discount for lack of marketability (DLOM)	25%
Estimated per share present value of marketable common stock (before DLOM)	$ 0.15

July 23, 2012 valuation

For the contemporaneous valuation at July 23, 2012, we used a hybrid of the probability-weighted expected return method, or PWERM, and the OPM, which we refer to as the hybrid method. Under the PWERM, share value is derived from the probability-weighted present value of expected future investment returns, considering possible outcomes available to us, as well as the economic and control rights of each share class. Our July 23, 2012 valuation considers two possible outcomes: an IPO and a later, unspecified liquidity event. The hybrid method is a PWERM where the values in one of the scenarios is calculated using an OPM. The hybrid method considers one IPO scenario and one OPM scenario. For the OPM scenario, the type of liquidity event, or outcome is undefined. In order to estimate the investment return for the IPO scenario, we considered the increase in value, or step-up, from the most-recent preferred round to the IPO price for a group of drug development companies which completed IPOs in the year preceding the appraisal date. We calculated the step-up as an annual rate of return. We applied this rate of return to our Series D preferred price to estimate its future value in the event of an IPO. For the IPO scenario, we assumed a future equity value equal to the product of the future value of Series D preferred stock times the number of common equivalent shares outstanding. The future equity value at the expected IPO date was allocated to each class of preferred stock and the common stock assuming conversion of all preferred classes to common. We estimated the time to an IPO date as 2.44 years based on our board of directors assessment of our prospects, our investors motivations and market conditions. We then discounted the values of each class of equity in the IPO scenarios at an appropriate risk-adjusted rate. We assumed risk-adjusted rates of 25% for the preferred shares and 30% for the common shares. We selected these risk-adjusted rates based on studies of the rates of return expected by venture capital investors, as presented in the AICPA Practice Aid.

In the OPM scenario, we applied the OPM back-solve method to solve for the equity value and corresponding value of common stock based on the $0.4983 per share price for the sale of Series D preferred stock in July 2012. Given the proximity to the Series D preferred stock financing, and the fact that the Series D preferred stock financing included and was led by

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unrelated investors, we believe the per share issuance price of the Series D preferred stock provides an indication of the fair value of our equity as of July 23, 2012. The values indicated for the preferred and common shares by the IPO scenario and the OPM scenario were probability weighted to calculate the weighted value as of the July 23, 2012 valuation date.

For the July 23, 2012 valuation, we estimated the fair value of our common stock by assigning an 85% weighting to the estimated fair value using the OPM back-solve method and a 15% weighting to the estimated fair value under the IPO scenario. We believe that the 85% weighting on the OPM back-solve method is appropriate due to the proximity of the issuance of our Series D preferred stock in July 2012 to the valuation date and the fact that the issuance included and was led by unrelated investors. The 15% weighting for the IPO scenario was deemed appropriate because at the time of the valuation, we believed that there was the possibility of following a successful Series D financing with an IPO.

Significant assumptions for the OPM include volatility, the risk-free rate, and the time to liquidity. We calculated annual rates of volatility based on weekly historical trading data for a group of guideline public companies. For the OPM scenario, the estimated time to liquidity was 3 years. The anticipated timing of a liquidity event was management s estimate in the event our planned IPO does not occur. We used the yield on three-year U.S. Treasuries as a risk-free rate.

We applied a discount for lack of marketability to the value indicated for our common stock. We lowered our estimate of the discount for lack of marketability to 20% based on our perception of our improved prospects for an IPO.

The following table summarizes the significant assumptions used in the hybrid method to determine the fair value of our common stock of $0.14 as of July 23, 2012:

July 23, 2012 valuation	**IPO**	**OPM**
Key assumptions		
Probability weighting	15%	85%
Liquidity date	1/1/2015	7/23/2015
Weighted-average cost of capital	25%	NA
Annual volatility	NA	70%
Risk-free interest rate	NA	0.3%
Discount for lack of marketability (DLOM)	20%	20%
Estimated per share present value of marketable common stock (before DLOM and probability weighting)	$ 0.31	$ 0.15

The estimated per share fair value of our common stock calculated in our valuation as of July 23, 2012 of $0.14 per share increased from the April 15, 2012 valuation of $0.11 per share primarily due to the following factors:

- our improved financial position resulting from the issuance of 120.4 million shares in July 2012 of our Series D preferred stock for an aggregate purchase price of $60.0 million;
- regulatory feedback from the FDA on the design of our Phase II/III Lenti-D study;
- regulatory feedback from the FDA on the nonclinical, manufacturing and clinical design of our Phase I/II LentiGlobin study;

filing of our clinical trial application, or CTA, in France for our Phase I/II LentiGlobin study; and

receipt of orphan drug designation for our Lenti-D program in the United States and European Union.

December 31, 2012 valuation

For the contemporaneous valuation at December 31, 2012, we used the hybrid method with one IPO scenario and one OPM scenario. As an indicator of value for the IPO scenario, we considered the increase in value, or step-up, from the most recent preferred round to the IPO price for a group of drug development companies which completed IPOs in the year preceding the appraisal date. We calculated the step-up as an annual rate of return. We applied this rate of return to our Series D preferred price to estimate its future value in the event of an IPO. For the IPO scenario, we assumed a future equity value equal to the product of the future value of Series D preferred stock times the number of common equivalent shares outstanding. The future equity value at the expected IPO date was allocated to each class of preferred stock and the common stock assuming conversion of all preferred classes to common. We estimated the time to an IPO date as one year based on our board of directors assessment of our prospects, our investors motivations and market conditions. We then discounted the values of each class of equity in the IPO scenarios at an appropriate risk-adjusted rate. We assumed risk-adjusted rates of 25% for the preferred shares and 30% for the common shares. We selected these risk-adjusted rates based on studies of the rates of return expected by venture capital investors, as presented in the AICPA Practice Aid. In the OPM scenario, we assumed an equity value equal to the present value of our equity in a future IPO.

For the December 31, 2012 valuation, we estimated the fair value of our common stock by assigning a 60% weighting to the estimated fair value using the OPM and a 40% weighting to the estimated fair value under the IPO scenario. We deemed the 40% weighting of our IPO scenario appropriate because of our progress since July 2012 in preparing for a potential IPO, which included advancements of our negotiations with a potential partner, completion of GMP-grade vector lots, qualification of a transduction manufacturing facility, advancement of our IND and CTA applications and engagement in initial discussions with underwriters.

Significant assumptions for the OPM include volatility, the risk-free rate, and the time to liquidity. We calculated annual rates of volatility based on weekly historical trading data for a group of guideline public companies. For the OPM scenario, the estimated time to liquidity was 2.56 years. The anticipated timing of a liquidity event was management s estimate in the event our planned IPO does not occur. We used the yield on three-year U.S. Treasuries as a risk-free rate.

We applied a discount for lack of marketability to the value indicated for our common stock. We lowered our estimate of the discount for lack of marketability to 10% based on our perception of the company s improved prospects for an IPO.

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The following table summarizes the significant assumptions used in the hybrid method to determine the fair value of our common stock of $0.29 as of December 31, 2012:

December 31, 2012 valuation	IPO	OPM
Key assumptions		
Probability weighting	40%	60%
Liquidity date	12/31/2013	7/23/2015
Weighted-average cost of capital	25%	NA
Annual volatility	NA	71%
Risk-free interest rate	NA	0.4%
Discount for lack of marketability (DLOM)	10%	10%
Estimated per share present value of marketable common stock (before DLOM and probability weighting)	$ 0.48	$ 0.22

The estimated per share fair value of our common stock calculated in our valuation as of December 31, 2012 of $0.29 per share increased significantly from the July 23, 2012 valuation of $0.14 per share. This is primarily due to the following factors:

- potential partnership with a leading pharmaceutical company that would extend our platform into oncology indication;
- increased probability of taking our Company public;
- successful manufacturing of two GMP-grade vector lots for our Lenti-D and LentiGlobin programs;
- successful completion of our LentiGlobin transduction manufacturing qualification at a centralized CRO;
- CTA approval of our ß-thalassemia and SCD study in France;
- filing of an IND for our ß-thalassemia program in the United States; and
- receipt of a $9.3 million award from CIRM to fund our U.S. LentiGlobin study.

March 31, 2013 valuation

For the contemporaneous valuation at March 31, 2013, we used the hybrid method with one IPO scenario and one OPM scenario. As an indicator of value for the IPO scenario, we considered the increase in value, or step-up, from the most recent preferred round to the IPO price for a group of drug development companies which completed IPOs in the five quarters preceding the appraisal date. We calculated the step-up as an annual rate of return. We applied this rate of return to our Series D preferred price to estimate its future value in the event of an IPO. For the IPO scenario, we assumed a future equity value equal to the product of the future value of Series D preferred stock times the number of common equivalent shares outstanding. The future equity value at the expected IPO date was allocated to each class of preferred stock and the common stock assuming conversion of all preferred classes to common. We estimated the time to an IPO date as 0.42 years based on our board of directors assessment of our prospects, our investors motivations and market conditions. We then discounted the values of each class of equity in the IPO scenarios at an appropriate risk-adjusted rate. We assumed risk-adjusted rates of 25% for the

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preferred shares and 30% for the common shares. We selected these risk-adjusted rates based on studies of the rates of return expected by venture capital investors, as presented in the AICPA Practice Aid. In the OPM scenario, we assumed an equity value equal to the present value of our equity in a future IPO.

For the March 31, 2013 valuation, we estimated the value of our common stock by assigning a 30% weighting to the estimated value using the OPM and a 70% weighting to the estimated fair value under the IPO scenario. We deemed the 70% weighting of our IPO scenario appropriate because of our progress since December 2012 in preparing for a potential IPO which included entering into a strategic collaboration with Celgene, further advancement of our IND applications, including effectiveness of the IND for our LentiGlobin program, and the filing of our initial registration statement.

Significant assumptions for the OPM include volatility, the risk-free rate, and the time to liquidity. We calculated annual rates of volatility based on weekly historical trading data for a group of guideline public companies. For the OPM scenario, the estimated time to liquidity was 2.31 years. The anticipated timing of a liquidity event was management s estimate in the event our planned IPO does not occur. We used the yield on two-year U.S. Treasuries as a risk-free rate.

We applied a discount for lack of marketability to the value indicated for our common stock. We estimated the discount for lack of marketability to be 10% based on our perception of our prospects for an IPO.

The following table summarizes the significant assumptions used in the hybrid method to determine the fair value of our common stock of $0.43 as of March 31, 2013:

March 31, 2013 valuation	**IPO**	**OPM**
Key assumptions		
Probability weighting	70%	30%
Liquidity date	8/31/2013	7/23/2015
Weighted-average cost of capital	25%	NA
Annual volatility	NA	72%
Risk-free interest rate	NA	0.3%
Discount for lack of marketability (DLOM)	10%	10%
Estimated per share present value of marketable common stock (before DLOM and probability weighting)	$ 0.56	$ 0.27

The estimated per share fair value of our common stock calculated in our valuation as of March 31, 2013 of $0.43 per share increased from the December 31, 2012 valuation of $0.29 per share. This is primarily due to the following factors:

- effectiveness of the IND for our LentiGlobin program in the United States;
- filing of an IND for our Lenti-D program in the United States;
- initial submission of our confidential draft registration statement on Form S-1 that increases the likelihood of a near-term liquidity event; and
- entering into a strategic collaboration with Celgene in March 2013 to discover, develop and commercialize novel, disease-altering gene therapies in oncology.

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Initial public offering price

In consultation with the underwriters for this offering, we determined the estimated price range for this offering, as set forth on the cover page of this prospectus. The midpoint of the price range is $ per share. In comparison, our estimate of the fair value of our common stock was $ per share as of . We note that, as is typical in IPOs, the estimated price range for this offering was not derived using a formal determination of fair value, but was determined by negotiation between us and the underwriters. Among the factors that were considered in setting this range were the following:

- an analysis of the typical valuation ranges seen in recent IPOs for companies in our industry;
- the general condition of the securities markets and the recent market prices of, and the demand for, publicly traded common stock of generally comparable companies;
- an assumption that there would be a receptive public trading market for pre-commercial biotechnology companies such as us; and
- an assumption that there would be sufficient demand for our common stock to support an offering of the size contemplated by this prospectus.

The midpoint of the estimated price range for this offering reflects an increase over the estimated valuation as of of $ per share. Investors should be aware of this difference and recognize that the price range for this offering is in excess of our prior valuations. Further, investors are cautioned not to place undue reliance on the valuation methodologies discussed above as an indicator of future stock prices. We believe the difference may be due to the following factors:

- The initial offering price range necessarily assumes that this offering has occurred, a public market for our common stock has been created and that our preferred stock has converted into common stock in connection with this offering and, therefore, excludes the marketability or illiquidity discounts associated with the timing or likelihood of an initial public offering, the superior rights and preferences of our preferred stock and the alternative scenarios considered in the contemporaneous valuations over the past two years.
- In the public markets we believe there are investors who may apply more qualitative valuation criteria to certain of our clinical assets than the valuation methods applied in our valuations.
- The price that investors are willing to pay in this offering, for which the price range is intended to serve as an estimate, may take into account other things that have not been expressly considered in our prior valuations, are not objectively determinable and that valuation models are not able to quantify.

Investors should be cautioned that the midpoint of the price range set forth on the cover of this prospectus does not necessarily represent the fair value of our common stock, but rather reflects an estimate of the offer price determined in consultation with the underwriters.

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There are significant judgments and estimates inherent in the determination of these valuations. These judgments and estimates include assumptions regarding our future performance, including the successful enrollment and completion of our clinical studies as well as the determination of the appropriate valuation methods. If we had made different assumptions, our stock-based compensation expense could have been different. The foregoing valuation methodologies are not the only methodologies available and they will not be used to value our common stock once this offering is complete. We cannot make assurances as to any particular valuation for our common stock. Accordingly, investors are cautioned not to place undue reliance on the foregoing valuation methodologies as an indicator of future stock prices.

Convertible preferred stock warrants

As of March 31, 2013, we had warrants outstanding to purchase shares of Series A-1 and Series B preferred stock. Freestanding warrants that are related to the purchase of redeemable preferred stock are classified as liabilities and recorded at fair value regardless of the timing of the redemption feature or the redemption price or the likelihood of redemption. The warrants are subject to re-measurement at each balance sheet date and any change in fair value is recognized as a component of other income (expense), net. We measure the fair value of our warrant liability using a Black-Scholes option pricing model. Any modifications to the warrant liability are recorded in earnings during the period of the modification. The significant assumptions used in estimating the fair value of our warrant liability include the exercise price, volatility of the stock underlying the warrant, risk-free interest rate, estimated fair value of the preferred stock underlying the warrant, and the estimated life of the warrant.

As a result of the revision of the terms of our Series A-1 preferred stock upon the Series D financing, the redemption feature in the Series A-1 preferred stock is no longer present. Due to this change, we re-evaluated whether the warrants to purchase Series A-1 preferred stock represented a liability. Because the Series A-1 preferred stock does not contain any redemption feature or preference in liquidation, we concluded that the warrant should be classified as permanent equity. On the date of reclassification, we performed a final valuation of the Series A-1 warrants, with the change in value recorded to other income (expense), net. The fair value of the warrants was then reclassified to additional paid in capital.

Pursuant to the terms of these warrants, upon the conversion of the class of preferred stock underlying the warrant, the warrants automatically become exercisable for shares of our common stock based upon the conversion ratio of the underlying class of preferred stock. The consummation of this offering will result in the conversion of all classes of our preferred stock into common stock. Upon such conversion of the underlying classes of preferred stock, the remaining warrants to purchase Series B preferred stock will be classified as a component of equity and no longer be subject to re-measurement.

Emerging growth company status

The Jumpstart our Business Startups Act of 2012, or the JOBS Act, permits an emerging growth company such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies. We are choosing to opt out of this provision and, as a result, we will comply with new or revised accounting standards as required when they are adopted. This decision to opt out of the extended transition period under the JOBS Act is irrevocable.

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Recently adopted accounting pronouncements

In February 2013, the FASB issued guidance to provide information about the amounts reclassified out of accumulated other comprehensive income, or AOCI, by component. An entity is required to present, either on the face of the financial statements or in the notes, significant amounts reclassified out of AOCI by the respective line items of net income, but only if the amount reclassified is required to be reclassified in its entirety in the same reporting period. For amounts that are not required to be reclassified in their entirety to net income, an entity is required to cross-reference to other disclosures that provide additional details about those amounts. On January 1, 2013, we adopted this standard, which had no impact on our financial position or results of operations.

In June 2011, the FASB issued an amendment to the accounting guidance for presentation of comprehensive income. Under the amended guidance, a company may present the total of comprehensive income, the components of net income, and the components of other comprehensive income either in a single continuous statement of comprehensive income or in two separate but consecutive statements. In either case, a company is required to present each component of net income along with total net income, each component of other comprehensive income along with a total for other comprehensive income, and a total amount for comprehensive income. The amendment is effective for fiscal years ending, and interim periods within those years, beginning after December 15, 2011, and is applied retrospectively. We adopted this amendment in the accompanying financial statements by presenting comprehensive income in one consecutive statement along with net loss.

In May 2011, the FASB issued amended guidance on fair value measurements. This newly issued accounting standard clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. This accounting standard was effective on a prospective basis for annual and interim reporting periods beginning on or after December 15, 2011. The adoption of this standard has not had a material impact on our financial position or results of operations.

Results of operations

Comparison of the three months ended March 31, 2012 and 2013 (unaudited)

Three months ended March 31,			**Increase**
(in thousands)	**2012**	**2013**	**(Decrease)**
	(unaudited)		
Revenue:			
Collaboration revenue	$	$ 1,042	$ 1,042
Research and license fees	85	85	
Total revenue	85	1,127	1,042
Expenses:			
Research and development	3,858	5,284	1,426
General and administrative	1,363	2,324	961
Total expenses	5,221	7,608	2,387
Loss from operations	(5,136)	(6,481)	(1,345)
Other income (expense), net	68	(63)	(131)
Net loss	$ (5,068)	$ (6,544)	$ (1,476)

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Revenue. Revenue was $1.0 million for the three months ended March 31, 2013, compared to $0.1 million for the three months ended March 31, 2012. The increase of $1.0 million from $0.1 million is due to the Celgene collaboration. In the three months ended March 31, 2013, we recorded $1.0 million in recognition of amounts allocated 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 $0.1 million of research fees.

Research and development expenses. Research and development expenses were $5.3 million for the three months ended March 31, 2013, compared to $3.9 million for the three months ended March 31, 2012. The increase was primarily due to a $0.4 million increase in employee- and contractor-related expenses to support increased development activities associated with three clinical studies planned to commence in 2013 and an $0.8 million increase in clinical start-up activities related to our LentiGlobin program.

General and administrative expenses. General and administrative expenses were $2.3 million for the three months ended March 31, 2013, compared to $1.4 million for the three months ended March 31, 2012. The increase in spending is primarily due to $0.6 million of employee- and contractor-related expenses to support corporate operational activities, including $0.3 million of consultant costs incurred in connection with preparing for this offering.

Other income (expense), net.

Other income (expense), net was $(0.1) million for the three months ended March 31, 2013, compared to $0.1 million for the three months ended March 31, 2012. The decrease was primarily due to the re-measurement of the redeemable convertible preferred stock warrants and foreign currency losses.

Comparison of the years ended December 31, 2011 and 2012

Year ended December 31,			**Increase**
(in thousands)	**2011**	**2012**	**(Decrease)**
Revenue	$ 882	$ 340	$ (542)
Expenses:			
Research and development	11,409	17,210	5,801
General and administrative	4,615	6,846	2,231
Total expenses	16,024	24,056	8,032
Loss from operations	(15,142)	(23,716)	(8,574)
Other income (expense), net	(456)	46	502
Net loss	$ (15,598)	$ (23,670)	$ (8,072)

Revenue. We recorded $0.3 million research fee revenue for the year ended December 31, 2012. For the year ended December 31, 2011, we recorded $0.9 million in revenue consisting of $0.3 million research fees, $0.3 million license fees, and $0.2 million grant revenue (a tax incentive from the Commonwealth of Massachusetts).

Research and development expenses. Research and development expenses were $17.2 million for the year ended December 31, 2012, compared to $11.4 million for the year ended December 31, 2011, an increase of $5.8 million. The increase was primarily due to:

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$2.8 million increase for clinical supply manufacturing and drug product process development activities in preparation for the ALD-102, HGB-204, and HGB-205 clinical studies planned for 2013;

$1.1 million increase to employee and contractor-related expenses to support the increased development activities in 2012 in anticipation of the three clinical studies planned for 2013;

$0.8 million increase in lab supplies, assay transfer and validation activities to support clinical supply and process development activities;

$0.7 million increase in consulting fees to support regulatory filing and other clinical start-up activities; and

$0.3 million increase in license and milestone fees paid to third parties.

General and administrative expenses. General and administrative expenses were $6.8 million for the year ended December 31, 2012, compared to $4.6 million for the year ended December 31, 2011. The increase of $2.2 million was due primarily to an increase of $1.4 million in professional fees, $0.6 million in employee and contractor-related expenses to support corporate operational and business development activities and $0.5 million in office and facility expenses, which was partially offset by a decrease in market study-related expenses.

Other income (expense), net. Other income (expense), net, was $0.05 million for the year ended December 31, 2012, compared to $(0.5) million for the year ended December 31, 2011, an increase of approximately $0.5 million. The increase was primarily due to revaluation of the redeemable convertible preferred stock warrants of $0.4 million and $0.1 million of currency losses.

Liquidity and capital resources

We have incurred losses and cumulative negative cash flows from operations since our inception in April 1992, and as of March 31, 2013, we had an accumulated deficit of $79.9 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, convertible notes and warrants to purchase common stock. In addition, in October 2012, we were awarded a $9.3 million grant from CIRM to fund our U.S. LentiGlobin study. This grant will be issued in quarterly installments and is expected to be utilized over a four-year period starting in the second quarter of 2013. In March 2013, we entered into a strategic collaboration with Celgene to discover, develop and commercialize novel, disease-altering gene therapies in oncology. This collaboration has an initial term of three years, and Celgene has made a $75 million up-front, non-refundable cash payment to us as consideration for entering into the collaboration. As of March 31, 2013, we had cash and cash equivalents of approximately $131.8 million. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. Currently, our funds are held in money market mutual funds consisting of U.S. government-backed securities.

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Cash flows

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

(in thousands)	Year ended December 31, 2011	2012	Three months ended March 31, 2012	2013
			(unaudited)	
Net cash provided by (used in):				
Operating activities	$ (12,217)	$ (21,044)	$ (6,200)	$ 66,018
Investing activities	(3,964)	2,599	3,175	(812)
Financing activities	32,435	59,852		(381)
Net (decrease) increase in cash and cash equivalents	$ 16,254	$ 41,407	$ (3,025)	$ 64,825

Operating activities. The significant increase in cash provided by operating activities for the three months ended March 31, 2013, compared to the three months ended March 31, 2012, is primarily due to the up-front payment related to the Celgene collaboration agreement. The significant increase in cash used in operating activities for the year ended December 31, 2012, compared to the year ended December 31, 2011, is primarily due to an increase in research and development expenses as we continue the development of our Lenti-D and LentiGlobin product candidates, which includes an increase in personnel related costs, process development and manufacturing activities. In addition, general and administrative expenses increased due to an increase in administrative personnel as well as professional and facility-related spending, offset by an increase in accrued expenses. The use of cash in all periods resulted primarily from our net losses adjusted for non-cash charges and favorable changes in components of working capital.

The net cash provided by operating activities was $66.0 million for the three months ended March 31, 2013, and consisted primarily of a net loss of $6.5 million adjusted for non-cash items including stock-based compensation expense of $0.7 million and depreciation of $0.1 million and a net increase in operating assets and liabilities of $71.7 million. The significant items in the change in operating assets and liabilities include an increase in deferred revenue of $73.9 million due to the up-front payment related to the Celgene collaboration partially offset by an increase in prepaid expenses and other current assets of $1.1 million and a decrease in accounts payable of $0.6 million and a decrease in accrued expenses and deferred rent of $0.5 million.

The net cash used in operating activities was $6.2 million for the three months ended March 31, 2012, and consisted primarily of a net loss of $5.1 million adjusted for non-cash items including stock-based compensation expense of $0.2 million and depreciation of $0.1 million and a net decrease in operating assets and liabilities of $1.3 million. The significant items in the change in operating assets and liabilities include decreases in accounts payable of $1.1 million and deferred revenue of $0.1 million and an increase in prepaid expenses and other current assets of $0.5 million slightly offset by an increase in accrued expenses and other liabilities of $0.4 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.

The net cash used in operating activities was $12.2 million for the year ended December 31, 2011, and consisted primarily of a net loss of $15.6 million adjusted for non-cash items including stock-based compensation expense of $0.8 million, re-measurement of warrants of $0.4 million, and depreciation of $0.2 million and a net increase in operating assets and liabilities of $1.9 million. The significant items in the change in operating assets and liabilities include increases in accounts payable of $0.9 million, accrued expenses and other liabilities of $0.4 million, and deferred revenues of $1.0 million, slightly offset by a decrease in prepaid expenses and other current assets of $0.3 million.

Investing activities. Net cash provided by (used in) investing activities consisted of purchases of fixed assets, purchases of marketable securities, and proceeds from the sale of marketable securities. Net cash used in investing activities for the three months ended March 31, 2013 was $0.8 million and consisted primarily of purchases of property and equipment. Net cash provided by investing activities for the three months ended March 31, 2012 was $3.2 million and consisted of proceeds from the sale of marketable securities of $3.5 million slightly offset by purchases of property and equipment of $0.3 million. 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. Net cash used in investing activities for the year ended December 31, 2011, was $4.0 million and was comprised primarily of purchases of marketable securities of $5.3 million, slightly offset by proceeds from the sale of marketable securities of $1.8 million and the purchases of property and equipment of $0.4 million.

Financing activities. Net cash used in financing activities for the three months ended March 31, 2013 was $0.4 million and consisted primarily of accumulated issuance costs related to our planned initial public offering. Net cash provided by financing activities for the year ended December 31, 2012 is the result of the sale of 120.4 million shares of our Series D preferred stock for net proceeds of $59.8 million. Net cash provided by financing activities for the year ended December 31, 2011 is the result of the issuance and sale of 39.9 million shares of our Series C preferred stock for net proceeds of $14.9 million, and the issuance and sale of 53.6 million shares of the second tranche of our Series B preferred stock for net proceeds of $17.5 million for aggregate net proceeds of $32.4 million.

Operating capital requirements

To date, we have not generated any revenue from product sales. We do not know when, or if, we will generate any revenue from product sales. We do not expect to generate significant revenue from product sales unless and until we obtain regulatory approval of and commercialize one of our current or future product candidates. We anticipate that we will continue to generate losses for the foreseeable future, and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize any approved products. We are subject to all of the risks incident in the development of new gene therapy products, and we may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. Upon the closing of this offering, we expect to incur additional costs associated with

operating as a public company. We anticipate that we will need substantial additional funding in connection with our continuing operations.

We believe that the net proceeds from this offering and our existing cash and cash equivalents will be sufficient to fund our projected operating requirements through at least the end of 2015. However, we may require additional capital for the further development of our existing product candidates and may also need to raise additional funds sooner to pursue other development activities related to additional product candidates.

Until we can generate a sufficient amount of revenue from our products, if ever, we expect to finance future cash needs through public or private equity or debt offerings. Additional capital may not be available on reasonable terms, if at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates. If we raise additional funds through the issuance of additional debt or equity securities, it could result in dilution to our existing stockholders, increased fixed payment obligations and these securities may have rights senior to those of our common stock. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, 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. Any of these events could significantly harm our business, financial condition and prospects.

Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of clinical studies for our products, including our Phase II/III Lenti-D study and our Phase I/II LentiGlobin studies;
- the outcome, timing and cost of regulatory approvals by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than those that we currently expect;
- the ability of our product candidates to progress through clinical development successfully;
- the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- our need to expand our research and development activities;
- our need and ability to hire additional personnel;
- our need to implement additional infrastructure and internal systems;
- the effect of competing technological and market developments; and
- the cost of establishing sales, marketing and distribution capabilities for any products for which we may receive regulatory approval.

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If we cannot expand our operations or otherwise capitalize on our business opportunities because we lack sufficient capital, our business, financial condition and results of operations could be materially adversely affected.

Contractual obligations and commitments

The following table summarizes our contractual obligations at December 31, 2012.

(in thousands)	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
Operating lease obligations(1)	$ 1,885	$ 831	$ 841	$ 213	$

(1) We lease office space at 840 Memorial Drive in Cambridge, Massachusetts under a noncancelable operating lease that expires on March 31, 2015.

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 an NDA, 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:

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

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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.

Off-balance sheet arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the Securities and Exchange Commission.

Quantitative and qualitative disclosures about market risks

We are exposed to market risk related to changes in interest rates. As of March 31, 2012 and 2013, we had cash and cash equivalents of $22.6 million and $131.8 million, respectively, primarily money market mutual funds consisting of U.S. government-backed 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. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our portfolio.

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Business

Overview

We are a clinical-stage biotechnology company focused on transforming the lives of patients with severe genetic and orphan diseases using gene therapy. Many diseases have a genetic aspect whereby a mutated gene linked to a disease is passed down from generation to generation and causes the disease. Gene therapy seeks to introduce a functional copy of the defective gene into a patient s own cells, a process called gene transfer. 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.

Each person s hereditary genetic material, or genome, is encoded by deoxyribonucleic acid, or DNA, in sequences of genetic code called genes. Genes, in turn, through a process called gene expression, produce proteins that perform a vast array of functions within all living organisms. 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 for example, too little or too much protein can be produced in the cell which can cause disease. Through gene transfer, a functional copy of the mutated gene is delivered to the patient s cells, thereby correcting the underlying genetic defect that causes aberrant gene expression.

In the gene transfer process, a functional gene is delivered and incorporated into a patient s cells through a delivery system called a vector, which are most commonly based on naturally-occurring viruses that have been modified to take advantage of the virus natural ability to introduce genes into cells. However, unlike naturally-occurring viruses, which replicate following infection of a target cell and have the capacity to infect new cells, viral vectors are modified to be non-replicating by deleting that portion of the viral genome responsible for replication. Gene transfer using a viral vector is called transduction and the resulting gene-modified cells are described as transduced cells. Transduction can be accomplished either via *ex vivo* or *in vivo* delivery. In the *ex vivo* approach, cells are gene-modified 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 suggest that the time is now for gene therapy to emerge as an 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 orphan diseases. We have assembled extensive expertise in viral vector design, manufacturing and gene transfer, a broad intellectual property estate, an experienced management team and a world-class group of scientific advisors and key opinion leaders. We refer to our viral vector and gene transfer technology and know-how as our gene therapy platform.

We and our scientific collaborators have generated what we believe is human proof-of-concept data for our gene therapy platform in two underserved diseases, each of which has been granted orphan drug status by U.S. and European regulatory authorities. We expect to initiate in late 2013 a Phase II/III clinical 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. We also expect to initiate in the second or third quarter of 2013, or mid-2013, Phase I/II clinical studies in the United States and Europe of our next most advanced product candidate, LentiGlobin, to evaluate its safety and efficacy in subjects with ß-thalassemia major and, in the European clinical study, sickle cell disease, or SCD, which are rare, hereditary blood disorders that often lead to severe anemia and shortened lifespans. We refer to the initiation of a clinical study as the time by which we have received all regulatory approvals necessary to commence a clinical study in accordance with a defined clinical protocol, we are under agreement with at least one clinical site to conduct the clinical study and we have begun to screen patients for enrollment in the clinical study. In addition, in March 2013, we announced a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel, disease-altering gene therapies in oncology.

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, a concept we refer to as the industrialization of gene therapy.

Utilizing our industrialized 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 and mortality, and is therefore typically only offered 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 to provide a potentially single-administration, transformative therapy, we believe the value proposition offered by our product candidates for patients, families, providers and payors would be significant.

Although our initial focus is in CCALD, ß-thalassemia and SCD, 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 and have the potential to be manufactured on a commercial scale reproducibly and reliably, as each new vector is produced using substantially the same process. We also take advantage of lentivirus ability to transduce HSCs more efficiently than other vectors, such as those derived from another virus used in gene therapy approaches, called adeno-associated virus, or AAV, which gives us the potential to address diseases in a variety of cell lineages that are derived from HSCs, such as microglia (useful for CCALD), red blood cells (useful for ß-thalassemia and SCD), T cells (useful for cancer and immunology) and others.

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

Gene therapy the time is now

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. Collectively, our 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 orphan 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 retinal disease, adrenoleukodystrophy, or ALD, ß-thalassemia, chronic lymphoid leukemia, hemophilia and Parkinson s disease.

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. Although the U.S. Food and Drug Administration, or the FDA, has not yet approved any human gene therapy product for sale, 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 gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee, or CTGTAC, to advise CBER on its reviews. In addition, the FDA has issued a growing body of clinical guidelines, chemical, manufacturing and control, or CMC, guidelines and other guidelines, all of which are intended to facilitate industry s development of gene therapy products.

First regulatory approval of a gene therapy product in the Western world. 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.

Growing investment from the pharmaceutical and biotechnology industries. Companies such as GlaxoSmithKline plc, Sanofi/Genzyme Corporation and BioMarin Pharmaceutical Inc. are currently advancing programs in gene therapy, and in 2012 Novartis AG

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announced a broad collaboration with the University of Pennsylvania to develop gene therapy products. In addition, Sanofi/Genzyme and Shire plc have made equity investments of $8.0 million in the aggregate in our Company, and we have partnered with Celgene Corporation in the field of oncology.

Increased interest in genetic screening. The growing market for both clinical and direct-to-consumer genetic testing and screening, including newborn screening initiatives for known hereditary diseases, points to increasing interest from patients and clinicians in therapeutic approaches that target specific genetic defects to treat disease.

Encouraged by these developments, we believe we are particularly well-positioned to drive the continued advancement of gene therapy technology in treating severe genetic and orphan diseases. We have assembled a leading position in the fields of gene therapy and severe genetic and orphan diseases, including extensive expertise in viral vector design, manufacturing and transduction, a broad intellectual property estate, an experienced management team and a world-class group of scientific advisors and key opinion leaders. Leveraging these capabilities, we have developed new, proprietary lentiviral vectors designed to more safely deliver our product candidates to patients, as well as improved transduction techniques to more efficiently effect gene transfer. We refer to our viral vector and transduction technology and know-how as our gene therapy platform. Our initial focus is on our two lead clinical programs in CCALD and ß-thalassemia major. However, we believe our gene therapy platform has broad applicability in a variety of severe genetic and orphan diseases beyond these initial indications, which we intend to explore selectively, either alone or through partnerships, such as our recently-announced collaboration with Celgene in the field of oncology.

Our gene therapy platform and process

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 of significant unmet medical need.

The historical challenges for gene therapy relate to the three factors on which the success of a gene therapy product is primarily based potency, efficiency and safety. The potency of a particular gene therapy product is measured by its effectiveness, which is based on successfully introducing the gene of interest into the target cells at a high enough frequency to achieve expression of the desired protein at a level sufficient to exert a therapeutic benefit. The efficiency of a gene therapy product is measured by the amount of product that is required to create the desired effect, the period of time it takes for the therapy to go into effect, and also the period of time over which the therapy is effective for a given dosage. Safety is evaluated based on the nature and severity of any side effects, complications, conditions or diseases that may result from introducing foreign materials into a person s body and cells. Until recently, there has been a lack of manufacturing and transduction infrastructure that would enable the delivery of these therapies in a reliable and reproducible manner and at a commercially viable scale.

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However, over the last several years, we have focused on and made significant investments in developing improved, next generation, viral vectors and manufacturing processes and procedures to address each of these issues.

These improvements include the following:

- We have developed proprietary viral vectors with improved potency, efficiency and safety over those vectors used historically, which in some cases raised serious safety concerns.

- We have developed proprietary vector manufacturing processes and techniques that produce a more purified and concentrated end product, as evidenced by the approximately 25 to 30-fold reduction in non-infectious viral particles as compared to viral vectors used in previous clinical studies (both ours and of others).

- We are investing in the development of mid- to large-scale manufacturing systems designed to be both reproducible and sustainable, with a view towards supporting our product candidates, if approved, at commercial scale.

We refer to these improvements as the industrialization of gene therapy manufacturing and production. We believe these improvements and our continuing investment in our manufacturing platform will enable us to develop best-in-class, next generation gene therapy products for severe genetic and orphan diseases.

Our proprietary lentiviral vectors

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 viral vectors based on other 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 integrate into a cell s DNA and thus require many viral events to transform a cell.

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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 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 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, with no known clinical events of insertional oncogenesis or cancer.

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 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.

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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. We believe there are numerous diseases associated with genetic abnormalities in cell types derived from HSCs that we can target using our gene therapy platform.

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 the viral vector will carry. The use of multiple plasmids is an important safety step designed to further prevent the resulting lentiviral vectors from being able to replicate and cause infection on their own.

2. A sample of 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, HSCs are extracted directly from the patient s bone marrow.

3. The lentiviral vector is mixed with the patient s isolated HSCs *ex vivo*. This leads to the insertion of the functional gene into the HSCs existing DNA, thus creating a pool of the patient s own, or autologous, gene-modified cells. The cells are then washed to remove any remnants of the viral vector or culture media. These gene-modified HSCs 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 corrected gene sequences. 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 12-24 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 in perpetuity 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

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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, 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, providers and payors would be significant.

Put simply, we believe we have developed next generation vectors with improved potency, efficiency and safety using a reproducible, scalable manufacturing process to address a variety of severe genetic and orphan diseases.

Our strategy

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 and orphan diseases. Central to this effort is a collective determination within our Company to provide these patients with hope for a better life in the face of limited or no long-term safe and effective treatment options. Specifically, our business strategy is based on the following principles:

Relentlessly focus on serving our patients. Our culture is rooted in a shared motivation to bring the transformative potential of gene therapy to patients in need. Our initial focus is on patients suffering from monogenic diseases such as CCALD, ß-thalassemia and SCD, as well as cancer; however, we believe there are many additional indications for which our technology may be applicable.

Be the world s biggest gene therapy geeks. We believe our people and our culture (based on the principles: b colorful, b cooperative, b yourself) will continue to be fundamental to our success. We will continue to build a professional team of employees, advisors and collaborators with deep and industry-leading experience in the discovery, development, manufacturing and commercialization of gene therapy technologies to treat severe genetic and orphan diseases. We believe our expertise in this field in terms of lentiviral vector design and gene therapy process industrialization will allow us to continue developing next generation technologies that will overcome some of the challenges that have historically complicated the use of gene therapy on a broader scale and allow for deployment in many underserved severe genetic and orphan disease markets. We will continue our efforts, which over the last several years have resulted in the production of early clinical proof-of-concept results in two diseases, the industrialization of the gene therapy process and the generation of significant intellectual property.

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Leverage our platform and technical expertise to build a gene therapy product engine for severe genetic and orphan diseases. We will continue to take advantage of the adaptability of our gene therapy platform in creating viral vectors and gene therapy products to address a broad range of genetically-defined diseases. Unlike other gene modification approaches that may require extensive optimization for each gene target or disease indication, each of our lentiviral vectors is produced using the same modified vector backbone and manufacturing system. This enables us to generate new product candidates relatively quickly by essentially swapping in the new gene of interest and assessing its potency and purity using standardized assays and tests. We believe our specific ability to design and manufacture lentiviral vectors quickly and reproducibly on a commercial scale will differentiate us from other gene therapy technologies and provides a strong competitive advantage in the long term.

Develop and commercialize drugs in our core disease areas and partner selectively to expand the scope of our pipeline. Our core disease areas are severe genetic and orphan diseases, such as CCALD and ß-thalassemia, that we believe to be good candidates for treatment with gene therapy. Given the relatively low prevalence of these diseases and the strong key opinion leader communities and patient advocacy groups around them, we believe we can serve these markets with a small targeted commercial infrastructure. The broad potential of our platform also presents an opportunity for us to selectively form collaborative alliances to expand our capabilities and product offerings into other therapeutic areas and potentially accelerate the development and commercialization of our products. For example, we recently announced a global strategic collaboration with Celgene to discover, develop and commercialize novel, disease-altering gene therapies in oncology.

Pursue indications with high unmet medical need and greater probability of clinical, regulatory and commercial success. Each of our three current core indications are severe diseases with high unmet medical need. We believe there is a strong rationale for treating diseases like these with gene therapy because their underlying genetic abnormality is well-characterized and can be addressed by correcting or inserting a single gene. Given the poor prognosis and current lack of corrective treatment options for these diseases, we believe our gene therapy product candidates may offer a potential single-treatment alternative for these patients and their families. Our gene therapy products, if successful, may offer a potentially superior long-term value proposition for our patients and the healthcare system more broadly, which will allow us to drive premium value while delivering patients life-altering treatments.

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Our product candidate pipeline

The following table summarizes key information on our development programs.

* The Phase II/III ALD-102 Study is our first clinical study of our current Lenti-D viral vector and product candidate. See Business Our Lenti-D product candidate.

** The Phase I/II HGB-205 and HGB-204 Studies are our first clinical studies of our current LentiGlobin viral vector and product candidate. See Business Our LentiGlobin product candidate.

Our most advanced product candidate is called Lenti-D, which we are developing to treat patients with ALD. We plan to initiate a Phase II/III clinical study of Lenti-D in the United States in late 2013, which we refer to as the ALD-102 Study, to examine the feasibility, safety and efficacy of Lenti-D in preserving neurological function and stabilizing cerebral demyelination in subjects with CCALD, the most severe form of ALD. We also expect to initiate sites outside the United States, pending approvals from the applicable regulatory authorities. If successful, and pending further discussion with the FDA, the results from the ALD-102 Study could potentially form the basis of a Biologics License Application, or BLA, submission to the FDA and a Marketing Authorization Application, or 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. Initial proof-of-concept data from a clinical study utilizing an approach similar to Lenti-D with an earlier generation lentiviral vector supplied by a third party were published in *Science* (2009).

Our next most advanced product candidate is called LentiGlobin, which we are developing to treat patients with ß-thalassemia and SCD. We are currently conducting a Phase I/II clinical study in France evaluating an earlier generation of our LentiGlobin vector for the treatment of ß-thalassemia major and SCD. Initial proof-of-concept data from this study were published in *Nature* (2010). We plan to initiate an extension of this study under a revised protocol for LentiGlobin, which we refer to as the HGB-205 Study, in mid-2013. We also plan to initiate a second Phase I/II clinical program in the United States for LentiGlobin, which we refer to as the HGB-204 Study, for ß-thalassemia major in mid-2013.

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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 will focus 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 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. 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 including neural cells in which they cause 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 incidence rate for ALD is approximately one in 20,000 newborn males, and the U.S. National Institute of Health, or NIH, estimates a prevalence of one in 20,000.

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 15 years and older. It is also very severe, with progression of neurologic symptoms that parallels the course of CCALD. ACALD accounts for approximately 5% of all patients diagnosed with ALD.

Limitations of current treatment options

There is a clear unmet medical need for patients with the neurologic forms 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 the properly 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 AMN and ACALD.

Allogeneic HSCT is typically 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 and 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 whose donor is not a matched sibling result in significant mortality rates. 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, for example as attention deficit hyperactivity deficit disorder. Newborn screening through a simple and inexpensive blood test is being developed to enable earlier detection of CCALD, but is not yet widely available. Based in part on the fact that several states 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. HSCs derived from the patient s own body are called autologous HSCs. We refer to autologous HSCs that have been modified to carry the functional copy of the ABCD1 gene as the final Lenti-D drug product, or our Lenti-D product candidate. 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 have had and continue to have extensive dialogue with the FDA, the EMA and other regulatory authorities and advisory bodies concerning the clinical advancement of our Lenti-D product candidate. These interactions include the following:

our Lenti-D product candidate has been granted orphan drug status by the FDA and the EMA for the treatment of CCALD;

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in 2010, the NIH s Office of Biotechnology Activities Recombinant DNA Advisory Committee, or the RAC, reviewed our draft protocol and its recommendations were incorporated into the final protocol and informed consent;

a type B pre-IND meeting with the FDA in 2010, during which meeting the FDA recommended we initiate a retrospective natural history of disease study to inform future clinical studies and provide guidance on the manufacturing, nonclinical and clinical development of our Lenti-D product candidate;

receipt of Scientific Advice regarding the design of the planned ALD-102 Study from the French agence nationale de sécurité du médicament et des produits de santé, or ANSM, in February 2011, from the EMA in May 2011, and from the United Kingdom Medicines and Healthcare Products Regulatory Agency, or MHRA, in May 2012;

a type C pre-IND meeting with the FDA in 2012, focused on the design of the planned ALD-102 Study;

an agreed Pediatric Investigation Plan, or PIP, with the EMA Pediatric Committee, or PDCO, in March 2013; and

an IND submission for our ALD-102 Study in March 2013, which IND is active as of April 2013.

We expect to initiate the ALD-102 Study in the United States in late 2013. We also expect to initiate sites outside the United States, pending approvals from the applicable regulatory authorities. If successful, and pending further discussion with the regulatory authorities, the results from the ALD-102 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 ALD-102 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.

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

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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 versus allogeneic HSCT-treated CCALD patient populations. The ALD-101 Study report was completed in March 2013.

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

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(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 transplant therapy due to the advanced stage of the disease.

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

Summary of findings

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

Untreated, 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.

	Mortality Rate*			
	NFS£ 1	**NFS > 1**	**Loes ³ 1 £ 9**	**Loes > 9**
Untreated Cohort	42%	85%	46%	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.

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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 ALD-102 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. Among the 72 patients in the untreated cohort, data were available regarding the presence of MFDs at 24 months post-CCALD diagnosis in 56 of these patients. Among these 56 patients, 29 patients (52%) developed at least one MFD throughout the data collection period. Of the 18 cases in the untreated cohort who were gadolinium positive, 13 (72%) had developed at least one MFD at 24 months from the time of their first gadolinium positive scan. We believe the finding that a large proportion of the untreated cohort with gadolinium enhancement progress to an MFD at 24 months provides an important reference point by which to assess the success of treatment with our Lenti-D product candidate. These observations support the requirement that subjects enrolled in the ALD-102 Study demonstrate gadolinium enhancement at baseline and support a primary endpoint based on the prevention of MFDs.

Gadolinium enhancement appears to be an objective, predictive measure of the likelihood of rapid progression. In the untreated cohort, of the 15 patients with scans that were gadolinium-positive and had repeat NFS assessments during the applicable observation period, most (12 of the15 patients) showed rapid progression of NFS scores, defined as an increase of greater than five points over the applicable observation period, with all 12 showing decline within six to 18 months. This observation supports the requirement that subjects enrolled in the ALD-102 Study demonstrate gadolinium enhancement at baseline. These patients would be expected to develop progressive disease without therapeutic intervention.

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. For the majority of patients in the treated cohort (63%), no MFD was present at 24 months post-HSCT. Allogeneic HSCT was also associated with resolution of gadolinium enhancement. Of those patients who would meet eligibility criteria for the ALD-102 study (baseline NFS of zero or one, gadolinium-positive at baseline, baseline Loes between 0.5 and nine, inclusive), three of 20 (15%) 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 (18%) patients, 10 of whom (83%) were transplanted with unrelated donor cells. Despite prophylaxis, the GVHD rate was 54%, including acute GVHD in 27 (42%) patients and chronic GVHD in 12 (18%) 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 ALD-102 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 ALD-102 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 planned ALD-102 Study, which we describe below.

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 study is ongoing although no new subjects are expected to be enrolled beyond the initial four boys.

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.

Subject One: Loes score stabilized at month 30 and remained stable through month 75.

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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.

At the top of the figure is a series of brain MRI images showing an example of progressive white matter disease in an untreated patient with CCALD. The expanding white in the images from left to right illustrates increasing demyelination in the brain and represents severe disease. The images below represent the baseline (left) and recent (right) brain MRI images from the four boys treated in the TG04.06.01 Study. In contrast to the extensive progressive white matter disease that might be seen in untreated CCALD, as shown at the top of the figure, the progression of white matter disease following treatment in the TG04.06.01 Study is more limited.

We believe these efficacy results are consistent with outcomes that would be expected following successful allogeneic HSCT. All four boys are 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 have shown 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 frequently seen following allogeneic HSCT, given the time it takes for transplant-derived microglial cells to populate the brain. Although neurologic deficits have occurred in these subjects post-treatment, we are encouraged by the fact that neurologic disease has stabilized in all four subjects.

Importantly, there have also been no reported incidents of gene therapy-related safety concerns in the TG04.06.01 Study. The infusion procedure was clinically uneventful for all four subjects, with all achieving successful engraftment within 15 days post-transplant. 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 provide 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 future ALD-102 Study. The design of the ALD-102 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, international trial with a different primary endpoint determined by analysis of the ALD-101 Study data 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 ALD-102 Study compared to what was achieved in the TG04.06.01 Study, which we believe will translate into improved clinical benefit by virtue of the increased expression of normally-functioning ALDP.

Phase II/III clinical study (the ALD-102 Study)

In April 2013, the FDA informed us that the IND we filed in March 2013 with the FDA for a Phase II/III clinical study to examine the feasibility, safety and efficacy of our Lenti-D product candidate is now active. We refer to this study as the ALD-102 Study. 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. Per the *FDA Guidance for Industry: Gene Therapy for Clinical Trials Observing Subjects for Delayed Adverse Events*, 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.

Our clinical trial recruitment plans involve a multi-faceted approach, including:

- clinical site community outreach programs;
- global patient referral and support programs to bring patients from across the world to existing clinical sites;
- gene therapy patient, family and physician education tools, including general gene therapy and ALD-specific websites and materials;
- ALD patient advocacy engagement and support; and
- continued publication of existing and future scientific and clinical ALD data.

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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 fifteen 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 matched sibling HSCT donor will be excluded from the study. We expect to initiate the ALD-102 Study in late 2013.

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 ALD-102 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 transplant. Thus, we expect the FDA 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.

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 HIV-1 virus; 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 ALD-102 Study would 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 will not require one or more additional clinical studies as a precursor to a BLA application. The FDA has advised us that the ALD-102 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.

Preclinical evaluation of our Lenti-D product candidate

We have completed a single-dose toxicology study of our Lenti-D product candidate in immunodeficient mice following a single intravenous administration. This study investigated the engraftment of normal human HSCs transduced with our Lenti-D vector and the reversibility of any toxicity following a 28 and 91 day post-treatment recovery period. The assessment of toxicity was based on mortality, clinical observations, body and organ weights, and anatomic pathology. In addition, engraftment of the HSCs was analyzed in the bone marrow of all the interim and main sacrifice animals by fluorescence-activated cell sorting and by polymerase chain reaction procedures.

Study results from the single dose toxicology study found no product candidate-related effects in body and organ weight, hematology or clinical chemistry parameters. In addition, histopathological evaluation revealed that there were no product candidate-related microscopic findings. There were no significant group differences (aside from slight individual animal

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variation) in cellularity of the bone marrow in treated control and test animals, as determined by light microscopy. Based upon the evaluation criteria used for the study, the Lenti-D drug product appeared to be well tolerated after single intravenous injection.

Additional potential clinical indications for Lenti-D

The ACALD and AMN subsets of the broader ALD patient population represent potential additional opportunities for our Lenti-D product candidate. Allogeneic HSCT has shown some early reported success in ACALD patients, suggesting autologous gene therapy with our Lenti-D product candidate may also be used to address these patients. AMN represents a population of heterogeneous patients with about 40% presenting with cerebral symptoms, however no known allogeneic HSCT studies have been conducted in the AMN population to provide evidence for a gene therapy based approach in the treatment of this disease. The risk-reward balance and safety risks associated with allogeneic HSCT have limited its use in treating ACALD and AMN patients, which may provide an opportunity to expand the use of our Lenti-D gene therapy product in these indications to increase interest in gene therapy for the treatment of other forms of ALD.

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. Symptoms of ß-thalassemia can include severe anemia, splenomegaly, marrow expansion, bone deformities and iron overload in major organs. 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 ($ß^0$) 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 $ß^0ß^0$ genotype as well as many with the $ß^0ß^+$ 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 $ß^0$ or $ß^+$ mutations.

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ß-thalassemia is concentrated in populations of Mediterranean, South and Southeast Asian and Middle Eastern descent. The total annual incidence of symptomatic individuals is estimated at one in 100,000 throughout the world and one in 10,000 people in the European Union. 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. This data is derived from a mandatory screening program for hemoglobinopathies in that state.

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 of approximately 9-10 g/dL. 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 hallmark symptoms of childhood ß-thalassemia major, however, often lead to a large 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 (which decreases or eliminates the cells in the bone marrow and blood), 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

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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 and SCD. Our approach involves the *ex vivo* insertion of a single codon variant of the normal ß-globin gene via an HIV-1 based 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 gene-modified HSCs as the final LentiGlobin drug product, or our LentiGlobin product candidate.

We have had and continue to have a comprehensive dialogue with the FDA, the EMA and other regulatory authorities and advisory bodies concerning the clinical advancement of our LentiGlobin product candidate. These interactions include the following:

- our LentiGlobin product candidate has been granted orphan drug designation by the FDA and the EMA and Fast Track status by the FDA;

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in 2012, the NIH s RAC reviewed our draft protocol and its recommendations were incorporated into the final protocol and informed consent;

a type B pre-IND meeting with the FDA in 2012 focused on the design of our planned HGB-204 Study and provided guidance on the manufacturing and nonclinical development with a view towards a future IND filing;

an IND submission for our HGB-204 Study in December 2012, which IND is effective as of January 2013;

a meeting with ANSM in November 2011 regarding the submission of a Clinical Trial Application, or CTA, with a revised clinical protocol to support the use of our current LentiGlobin vector in our planned HGB-204 Study, and confirming that no additional *in vivo* toxicology data would be required for the CTA submission; and

submission and approval of the CTA for the HGB-205 Study in 2012.

We expect to initiate our HGB-204 and HGB-205 clinical studies in mid-2013.

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).

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. Subject Three has remained transfusion-independent ever since (more than four years), even in light of regular blood withdrawals to eliminate iron accumulation in the body. Adverse events considered to be treatment related were all attributable to study procedures or myeloablative conditioning, but not the HPV569 drug product. One notable observation was the detection of partial clonal dominance of a common myeloid progenitor bearing an integrated vector in the third intron of the HMGA2 gene, which resulted in a relatively large proportion of the gene therapy modified cells being derived from a single clone in which the lentiviral vector had inserted into the HMGA2 gene. There was some initial concern that the observed clonal dominance might represent a pre-leukemic event, however there have been no adverse clinical consequences of this event, or any signs of

cancer, in over five years since the observation was made. In fact, the presence of the HMGA2 clone has steadily declined over time to the point that it is no longer the most common clone.

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. Therapeutic hemoglobin in reticulocytes was detectable by one month post-transplant. At two- and six-months post-transplant, therapeutic hemoglobin was expressed in 4.0% and 3.1% of reticulocytes, respectively. Subject Four is clinically stable, has fully engrafted and feels well. However, transfusion requirements remain unchanged at approximately monthly intervals with T87Q corrected globin stably expressed at levels substantially below those demonstrated by Subject Three at similar time points. Further follow-up is required to establish the complete trajectory of T87Q globin production and vector copy number. Adverse events considered to be treatment related were all attributable to study procedures or myeloablative conditioning, but not the HPV569 drug product.

We believe that achieving transfusion independence in Subject Three is a direct benefit of treatment with the HPV569 drug product, as we are not aware of any reported cases of spontaneous transfusion independence in patients with ß-thalassemia major. While successful allogeneic HSCT may achieve transfusion independence, the mortality risk of allogeneic HSCT in adults with ß-thalassemia major exceeds 20%, and for that reason it is not a standard therapeutic intervention for adult patients. The approach of using autologous gene-modified HSCs avoids the adverse consequences of immune incompatibility that are responsible for much of the mortality and morbidity associated with allogeneic HSCT.

We believe the efficacy and safety results of the LG001 Study provide 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 HGB-204 clinical studies. Additionally, with improvements we have introduced into the vector manufacturing and transduction processes, we expect to obtain a higher frequency of gene-therapy modified HSCs in the patients treated in the HGB-205 and HGB-204 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.

Phase I/II clinical study for ß-thalassemia major and sickle cell disease (the HGB-205 Study)

At the request of ANSM, in 2012 we submitted a CTA with a revised clinical protocol for the LG001 Study as a result of our decision to use our newer LentiGlobin BB305 vector for our clinical studies going forward. A preclinical evaluation of LentiGlobin BB305 showed that transduction efficiency was higher with the LentiGlobin BB305 vector as compared to the HPV569 vector used in the LG001 Study, resulting in higher expression of the therapeutic ß-globin protein in transduced cells, despite unchanged expression levels per vector copy. The CTA was accepted in 2012, resulting in an active study, now called the HGB-205 study, which we expect to initiate in France in mid-2013. This continuation study is a Phase I/II clinical study to examine the safety and efficacy of our LentiGlobin product candidate in up to seven additional subjects with a diagnosis of ß-thalassemia major or SCD. Study subjects must be between five and 35 years of age with a diagnosis of ß-thalassemia major or SCD. Those 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

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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 related donor. Subjects with a matched sibling allogeneic HSCT donor will be excluded from the study.

Our clinical trial recruitment plans for the HGB-205 Study involve a multi-faceted approach, including:

- clinical site community outreach programs;
- global patient referral and support programs to bring patients to existing clinical sites;
- clinical site expansion in areas of high epidemiology;
- gene therapy patient, family and physician education tools, including general gene therapy and ß-thalassemia and SCD specific websites and materials;
- ß-thalassemia and SCD patient advocacy engagement; and
- support and continued publication of existing and future ß-thalassemia and SCD scientific and clinical data.

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.

Phase I/II clinical study for ß-thalassemia major (the HGB-204 Study)

In December 2012, we submitted an IND with the FDA for a Phase I/II clinical study to examine the feasibility, safety and efficacy of our LentiGlobin product candidate. We refer to this study as the HGB-204 Study. The study is a single-dose, open-label, non-randomized, multi-site Phase I/II clinical study in the United States to evaluate the safety and efficacy of the LentiGlobin product candidate in increasing hemoglobin production and eliminating or reducing transfusion dependence following treatment. In January 2013, we were cleared to commence the study and we expect to initiate this study in mid-2013.

Our clinical trial recruitment plans for the HGB-204 Study involve a multi-faceted approach, including:

- clinical site community outreach programs;
- global patient referral and support programs to bring patients to existing clinical sites;
- clinical site expansion in areas of high epidemiology;

gene therapy patient, family and physician education tools, including general gene therapy and ß-thalassemia specific websites and materials;

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ß-thalassemia patient advocacy engagement; and

support and continued publication of existing and future ß-thalassemia scientific and clinical data.

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 who receive at least 100 mL/kg/year of pRBCs or greater than or equal to eight transfusions of pRBCs per year in each of the two years preceding enrollment. The subjects must also be eligible for allogeneic HSCT.

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

Preclinical evaluation of our LentiGlobin product candidate

Several nonclinical studies have been performed to support the use of our LentiGlobin BB305 vector. These studies were conducted in human HSCs isolated from patients with SCD and in *in vivo* mouse transplant models. In these studies, transduction efficiency was shown to be higher with the LentiGlobin BB305 vector as compared to the HPV569 vector, based on higher expression levels of the therapeutic ß-globin protein in cells transduced with this vector despite unchanged protein expression levels per vector copy. *In vivo* pharmacology and safety studies carried out in a mouse model for ß-thalassemia provided no evidence that our lentiviral vectors caused any adverse effects or alteration of bone marrow homeostasis in animals treated with cells transduced with either the HPV569 or BB305 vector. In two independent *in vitro* immortalization, or IVIM, assays, LentiGlobin BB305 vector showed a reduced risk of IVIM and genotoxicity in murine HSCs as compared to positive control vectors known to have significant oncogenic potential. Results of integration site analyses in mice treated with syngeneic bone marrow cells transduced with either LentiGlobin BB305 or HPV569 vectors revealed no signs for clonal outgrowth. The integration site profile of the two vectors was comparable and typical for HIV-1 based lentiviral vectors. Both vectors showed a large overlap of integration sites in identical common integration site regions. Although integration near oncogenes was, in general, increased in the analyzed vector samples compared to the theoretical random integration site data, there was no increase of integration sites near oncogenes in the post-transplant samples isolated from the bone marrow at necropsy compared to pre-transplant samples of transduced bone marrow.

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Previous preclinical experience with lentiviral gene therapy for sickle cell disease

In 2001, a preclinical proof-of-concept study, led by our scientific founder Dr. Philippe Leboulch and scientists at Harvard Medical School and the Massachusetts Institute of Technology, corrected sickle cell disease in mice using gene therapy. In the study, mice were bioengineered to contain a human gene that produced defective hemoglobin, causing SCD. HSCs containing the defective gene were removed from the bioengineered mice and gene-modified by the addition of an anti-sickling gene using a lentiviral vector. The modified gene (T87Q) produced ß-globin that gave rise to a modified normal hemoglobin molecule that prevented the sickling process. This gene construct is the same construct we use in our LentiGlobin product candidate. After adding the anti-sickling gene, the corrected marrow was then transplanted into other mice with SCD whose bone marrow had been removed by radiation. Ten months later, blood samples from the transplanted mice showed a high level of expression of the anti-sickling ß-hemoglobin gene. The results from this preclinical proof-of-concept study for SCD were published in *Science* (2001).

Manufacturing

Our gene therapy platform has two main components: lentiviral vector production and the target cell transduction process, which results in our finished 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 such functional gene of interest. The genetic material is delivered on multiple plasmids to reduce the odds of generating a replication-competent virus and improve the overall safety of this step of the procedure. 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 by a single chromatography step, concentrated and formulated

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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 currently in the process of 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 are currently transferring the new process to a contract manufacturer in compliance with Good Manufacturing Practices, or GMP, to accommodate future demand for our drug candidates, if approved, in their current indications as well as those beyond our initial focus.

Our target cell 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 our drug product 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 up to 40 hours 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.

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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.

Of note, our proprietary lentiviral vector manufacturing and HSC transduction processes utilize operations and equipment that are common to the biopharmaceutical industry. 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 orphan 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: 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 rapidly 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 plan to pursue 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 T cells and 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 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.

Adeno-associated viral (AAV) vector platform targeting other diseases: Our team has extensive historic experience with AAV research and development programs. There is extensive evidence in the scientific literature supporting the use of these vectors for *in vivo*

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applications. The unique properties of AAV vectors may offer advantages in some indications where lentiviral vectors might be less suited. For example, AAV vectors may be better suited for use in products delivered *in vivo* systematically. Our experience and know-how could be useful with an AAV platform in these additional disease settings and we expect to explore cautiously and opportunistically AAV product candidates that could provide a bolt-on platform and capability for us.

The graphic below represents an example of the breadth of potential applications of our gene therapy platform.

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 and orphan diseases. 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 will focus 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.

Under the terms of the collaboration, for any product candidate selected for development under the collaboration, we 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 will be governed by a joint steering committee, or JSC, formed by representatives from us and Celgene. The JSC will, among other activities, review the collaboration program, review and evaluate product candidates and approve 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 development and regulatory 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. We would do so under a written agreement, the form of which has not yet been agreed upon, although we have agreed upon certain material terms for such manufacturing and supply agreement. 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 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

Our agreement with Celgene provides that, effective upon completion of this offering, 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.

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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 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, processes to manufacture our lentivirus-based product candidates and other proprietary technologies and processes related to our lead product development candidates. As of the date of this prospectus, our patent portfolio includes the following:

- approximately 176 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 58 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 18 patents or patent applications that we own, including eight that are co-owned with MIT, related to vector manufacturing or production;
- approximately seven patents or patent applications that have been non-exclusively in-licensed from academic institutions and third parties related to vector manufacturing or production; and

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approximately 12 patents or patent applications that we own or have exclusively in-licensed from academic institutions and third parties related to therapeutic cellular products.

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 March 31, 2013, we had an exclusive license (from Pasteur Institute) to four issued U.S. patents and four pending U.S. applications. 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 March 31, 2013, we had an exclusive license (from RDF) to three 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 March 31, 2013, we owned one pending U.S. application and one pending Patent Cooperation Treaty, or PCT, application that is due for national stage entry in December 2013. We expect the composition of matter patent for the CCALD gene therapy vectors, if issued from the pending patent application and if the appropriate

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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 March 31, 2013, we co-owned one issued U.S. patent and two pending U.S. applications, 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 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. One aspect of the bluebird bio patent portfolio contains patents and patent applications directed to certain specific compositions of matter and improved methods for selecting and delivering transduced cells. As of March 31, 2013, we owned one pending PCT application that is due for national stage entry in July 2013. We expect any composition of matter or methods 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 2031 (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 2031 (worldwide, excluding possible patent term extensions). Another component of the bluebird bio patent portfolio includes the vector manufacturing platform and is potentially applicable to the CCALD, ß-thalassemia, SCD 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 March 31, 2013, we owned two U.S. provisional applications, which have nonprovisional filing bar dates in 2013, and two pending PCT applications, which are due for national stage entry in December 2013 and March 2014. 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).

In addition to the above, we have established expertise and development capabilities focused in the areas of preclinical research and development, manufacturing and manufacturing process scale-up, quality control, quality assurance, regulatory affairs and clinical trial design and implementation. We believe that our focus and expertise will help us develop products based on our proprietary intellectual property.

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

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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. 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 date in 2019 and 2020. 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 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. Beginning in April 2013, we will pay 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.

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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 2025.

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Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. While we believe that our proprietary asset estate and scientific expertise in the gene therapy field provide us with competitive advantages, we face potential competition from many different sources, including larger and better-funded pharmaceutical 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 Lenti-D and LentiGlobin product candidates, if approved. 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. We are also aware of some early-stage, preclinical efforts in academic centers to investigate the use of anti-oxidants for patients with AMN.

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 approval for its IND in 2012, and is actively recruiting 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, although to our knowledge no clinical studies have been initiated; and Sangamo BioSciences Inc., which has announced plans to investigate the use of zinc finger nuclease-mediated gene-correction techniques in hemoglobinopathies including ß-thalassemia, although to our knowledge no clinical studies have been initiated.

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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, and it can be assumed that the data from these studies will influence future utilization of this therapeutic modality. 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. There is also considerable interest from academic centers and biopharmaceutical companies to develop new therapies for SCD. A number of different 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., 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.

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.

Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. 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.

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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

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.

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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.

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

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

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

Phase I. The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

Phase II. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

Phase III. Clinical studies are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

Post-approval clinical studies, sometimes referred to as Phase IV clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor s initial receipt of the information. Phase I, Phase II and Phase III clinical studies may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB s requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH 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,

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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.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA s fee schedule, effective through September 30, 2013, the user fee for an application requiring clinical data, such as a BLA, is $1,958,800. PDFUA also imposes an annual product fee for biologics ($98,380) and an annual establishment fee ($526,500) on facilities used to manufacture prescription biologics. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

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.

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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.

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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. 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

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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, 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

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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. On April 10, 2013, President Obama released his proposed budget for fiscal year 2014 and proposed to cut this twelve-year period of exclusivity down to seven years. He also proposed to prohibit additional periods of exclusivity for brand biologics due to minor changes in product formulations, a practice often referred to as evergreening. 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.

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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 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, clinical study development 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

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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.

Facilities

Our corporate headquarters are located in Cambridge, Massachusetts. The facility we lease encompasses approximately 17,600 square feet of office and laboratory space. The lease for this facility expires on March 31, 2015, subject to our option to renew for up to one additional three-year term. We believe that our facility is sufficient to meet our needs and that suitable additional space will be available as and when needed.

Employees

As of March 31, 2013, we had 50 full-time employees, 13 of whom have Ph.D. or M.D. degrees. Of these full-time employees, 37 employees are engaged in research and development activities and 13 employees are engaged in finance, legal, human resources, facilities and general management. 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.

Legal proceedings

From time to time, we are subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, as of the date of this prospectus, we do not believe we are party to any claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

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Management

Executive officers, significant employees and directors

The following table sets forth information regarding our executive officers, significant employees and directors, as of March 31, 2013:

Name	Age	Position(s)
Executive Officers:		
Nick Leschly	40	President, Chief Executive Officer and Director
Jeffrey T. Walsh	47	Chief Operating Officer and Secretary
Mitchell H. Finer, Ph.D.	54	Chief Scientific Officer
David Davidson, M.D.	49	Chief Medical Officer
Linda C. Bain, CPA	42	Vice President, Finance and Business Operations and Treasurer
Significant Employees:		
Mark D. Angelino, Ph.D.	40	Vice President, Pharmaceutical Sciences
Richard E.T. Smith, Ph.D.	42	Vice President, Investor Relations
Faraz Ali	40	Vice President, Head of Program Management and Commercial Development
Cyrus Mozayeni	38	Sr. Director, Business Development
Kathleen Wilkinson	41	Sr. Director, Human Resources
Non-Management Directors:		
Daniel S. Lynch(1)(2)	55	Chairman of the Board
Wendy L. Dixon, Ph.D.(1)	57	Director
Steven Gillis, Ph.D.(1)	60	Director
John M. Maraganore, Ph.D.(2)	50	Director
Geert-Jan Mulder, M.D.(4)	46	Director
Dr. Axel Polack(3)	56	Director
David P. Schenkein, M.D.(3)	55	Director
Robert I. Tepper, M.D.(2)	57	Director

(1) Member of the audit committee.

(2) Member of the compensation committee.

(3) Member of the nominating and corporate governance committee.

(4) Dr. Mulder has indicated to us his intention to resign from our board of directors upon the consummation of this offering.

Nick Leschly has served as our president and chief executive officer since September 2010. Previously, he served as our interim chief executive officer from March 2010 to September 2010. Formerly a partner of Third Rock Ventures, L.P. since its founding in 2007, Mr. Leschly played an

integral role in the overall formation, development and business strategy of several of Third Rock s portfolio companies, including Agios Pharmaceuticals, Inc. and Edimer Pharmaceuticals, Inc. Prior to joining Third Rock, he worked at Millennium Pharmaceuticals, Inc., leading several early-stage drug development programs and served as the product and alliance leader for VELCADE. Mr. Leschly also founded and served as chief executive officer of MedXtend Corporation. He received his B.S. in molecular biology from Princeton University and his M.B.A. from Wharton Business School. We believe that Mr. Leschly s operation and historical experience with our Company gained from serving as our president, chief executive officer and member of the board of directors, combined with his experience in the venture capital industry and drug research and development qualify him to serve as a member of our board of directors.

Jeffrey T. Walsh has served as our chief operating officer since May 2011 and as our secretary since March 2013. Mr. Walsh has 25 years of experience in executive leadership positions with responsibility for finance, business development, commercial and business operations, strategic planning and legal functions with established and emerging public and private life sciences companies. From November 2008 to February 2011, Mr. Walsh served as chief business officer of Taligen Therapeutics, Inc. where he played a key role in the growth of the company and the ultimate sale of Taligen Therapeutics, Inc. to Alexion Pharmaceuticals, Inc. in January 2011. Mr. Walsh started his career at SmithKline Beecham Corporation in finance and worldwide business development roles. He subsequently held senior business development, finance and operations roles at PathoGenesis Corp. (acquired by Chiron Corporation), Allscripts Healthcare Solutions Inc., EXACT Sciences Corporation and Inotek Pharmaceuticals Corp. Mr. Walsh received his B.A. in sociology and economics from Yale University and his M.B.A. from the Kellogg Graduate School of Management at Northwestern University.

Mitchell H. Finer, Ph.D. has served as our chief scientific officer since March 2010. Prior to joining us, Dr. Finer served as senior vice president of development and operations for Novocell, Inc. (now ViaCyte, Inc.), a stem cell engineering company researching treatments for diabetes and other chronic diseases from November 2008 through March 2010. From July 2005 through November 2008, Dr. Finer served as chief executive officer of Intracel Holdings LLC. From June 2003 to June 2005, he held the position of president and chief executive officer of Genteric Inc., or Genteric, which filed a voluntary petition for reorganization under Chapter 11 of the U.S. bankruptcy code in August 2004. Previously, he had served as Genteric s chief scientific officer from November 2002 to June 2003 and as vice president of research and development for the Gencell division of Aventis Pharma (now Sanofi) from April 2002 to November 2002. He was also a founder and vice president of research for Cell Genesys Inc., and a founder of Abgenix, Inc. and Avalanche Biotechnologies, Inc. Dr. Finer received his B.A. in biochemistry and bacteriology from the University of California at Berkeley and his Ph.D. in biochemistry and molecular biology from Harvard University. He completed a postdoctoral fellowship at the Whitehead Institute for Biomedical Research.

David Davidson, M.D. has served as our chief medical officer since February 2012. Prior to joining us, Dr. Davidson served as a senior medical director at Genzyme Corporation, or Genzyme, where he led clinical research for programs in Phases I through IV across a wide range of therapeutic areas for more than a decade. Most recently, Dr. Davidson was the medical leader for Genzyme s gene therapy and Pompe disease enzyme replacement therapy programs. In addition to Dr. Davidson s translational medicine experience, he has also worked on a number of commercial products, including Fabrazyme and Myozyme/Lumizyme, and was integral in crafting the new drug application that resulted in the approval of Welchol. Prior to Genzyme, Dr. Davidson was a medical director at GelTex Pharmaceuticals Inc. Previously, he completed

clinical and research fellowships in infectious diseases at the Harvard Longwood Combined Infectious Diseases Program. Dr. Davidson received his B.A. from Columbia University and his M.D. from New York University School of Medicine. In addition, he completed an internal medicine internship, residency training and an endocrinology research fellowship at the University of Chicago Hospitals.

Linda C. Bain, CPA has served as our vice president of finance and business operations since October 2011 and as our treasurer since March 2013. Previously, she served as vice president of corporate finance at Genzyme from September 2008 to September 2011, at Fidelity Investments from September 2007 to September 2008 and a number of positions at AstraZeneca from May 2000 to September 2007. She received her B.S. from the University of the Orange Free State in South Africa.

Mark D. Angelino, Ph.D. has served as our vice president of pharmaceutical sciences since May 2012. Previously, Dr. Angelino served as senior director of research and development and Cambridge site head at Baxter Healthcare Corporation from December 2010 to May 2012 and as vice president of pharmaceutical development at Archemix Corporation from May 2008 to December 2010. Dr. Angelino received his B.S. in Chemical Engineering from The Cooper Union and his M.S. in chemical engineering practice and Ph.D. in chemical engineering from the Massachusetts Institute of Technology.

Richard E. T. Smith, Ph.D. has served as our vice president of investor relations since March 2013. From March 2012 to March 2013, Dr. Smith served as a consultant for a number of biotechnology companies. Previously, Dr. Smith served as vice president of investor relations and corporate communications at Pharmasset, Inc. from October 2008 until January 2012, when Pharmasset was acquired by Gilead Sciences. From May 2004 through August 2008, Dr. Smith was an equity research analyst at J.P. Morgan Securities covering biotechnology companies. Dr. Smith received his B.Sc. in Applied Zoology from the University of Leeds, his M.Sc. in Toxicology from the University of Surrey and his Ph.D. in Clinical Virology from the University of Oxford.

Faraz Ali has served as our vice president and head of program management and commercial development since May 2011. In 2011, he served as a consultant to Third Rock Ventures, L.P. From 2001 to 2010, Mr. Ali held a number of positions at Genzyme, including most recently, senior director of U.S. marketing and strategic planning of the personalized genetic health business unit from August 2006 to December 2010. Mr. Ali received his B.S. in electrical engineering from Stanford University and his M.B.A. from Harvard Business School.

Cyrus Mozayeni, M.D. has served as our senior director of business development since June 2010. Previously, he served as director of strategic/business development at PPD Dermatology (Magen Biosciences, Inc. until April 2009) from April 2007 to May 2010. Dr. Mozayeni received his B.S. in neuroscience from Brown University, his M.D. from the University of Virginia School of Medicine and his M.B.A. from the Kellogg Graduate School of Management at Northwestern University.

Kathleen Wilkinson has served as our senior director of human resources since November 2012. Previously, she served as human resources director of Adnexus Therapeutics from September 2009 to November 2012, consulted with Codon Devices Inc. from February 2009 to April 2009 and served as senior human resources director of Codon Devices from June 2007 to February 2009. Ms. Wilkinson received her B.A. in sociology from Harvard University.

Wendy L. Dixon, Ph.D. has served as a member of our board of directors since April 2013. In 2012, Dr. Dixon was a principal at Great Meadow Consulting LLC and in 2010, she served as senior

advisor at The Monitor Group. Since 2005, Dr. Dixon has advised and consulted and in some instances served as a member of the board of director for a number of biopharmaceutical companies, including Alkermes PLC, Incyte Corporation, Orexigen Therapeutics, Furiex Pharmaceuticals and formerly on Ardea Biosciences, Inc. (sold to AstraZeneca PLC in 2012) and Dentsply International. Dr. Dixon also served as Chief Marketing Officer and President of Global Marketing for Bristol-Myers Squibb and as a member of the CEO s Executive Committee from 2001 to 2009. She has had an over 30-year career in the pharmaceutical and biotechnology business, combining a technical background and experience in drug development and regulatory affairs with commercial responsibilities in building and leading organizations and launching and growing more than 20 pharmaceutical products including Tagamet, Fosamax, Singulair, Plavix, Abilify, Reyataz and Baraclude. From 1996 to 2001, she was Senior Vice President Marketing at Merck and prior to that she held executive management positions at West Pharmaceuticals, Osteotech and Centocor, and various positions at SmithKline and French (now GlaxoSmithKline) in marketing, regulatory affairs, project management and as a biochemist. Dr. Dixon received her B.Sc., M.Sc. and Ph.D. from the University of Cambridge (UK). We believe that, among other experience, qualifications, attributes and skills, Dr. Dixon s technical background in drug development, commercialization, marketing and regulatory affairs qualify her to serve as a member of our board of directors.

Steven Gillis, Ph.D. has served as a member of our board of directors since April 2011. Since 2005, Dr. Gillis has been a managing director at ARCH Venture Partners, a venture capital firm. From 1994 to 2005, Dr. Gillis served as chief executive officer and chairman of the board of directors of Corixa Corporation, which he co-founded in October 1994. Previously, Dr. Gillis served as a director, head of research and development, chief scientific officer and acting chief executive officer of Immunex Corporation, which he co-founded. As a former director and chairman of Trubion Pharmaceuticals, Inc., Dr. Gillis led its acquisition by Emergent BioSolutions in the fall of 2010. Dr. Gillis currently serves as a director of Accelerator Corporation, Allozyne, Inc., Pulmatrix, Inc., VLST Corporation and VBI Vaccines and serves as director and chairman of VentiRX Pharmaceuticals, Inc., Theraclone Sciences, Inc., Lycera Corp. and PhaseRx, Inc. Dr. Gillis received his B.A. in biology and English from Williams College and his Ph.D. in biological science from Dartmouth College. We believe that Dr. Gillis s experience in the venture capital industry, particularly with biotech and pharmaceutical companies, combined with his experience in molecular and tumor immunology, qualify him to serve as a member of our board of directors.

Daniel S. Lynch has served as chairman of our board of directors since May 2011, when he joined Third Rock Ventures, L.P., or Third Rock, as an entrepreneur-in-residence. Since October 2007, Mr. Lynch has advised and served as executive chair or member of the board of directors for a number of private biopharmaceutical companies, which include Stromedix, Inc. (until its acquisition by Biogen Idec in February 2012), Avila Therapeutics, Inc. (until its acquisition by Celgene Corporation in February 2012), BIND Biosciences, Inc., RaNA Therapeutics, Inc., Nimbus Discovery, LLC, Edimer Pharmaceuticals, Ember Therapeutics, Inc. and Blueprint Medicines, Inc. Previously, Mr. Lynch served as chief executive and chief financial officer of ImClone Systems Corporation, or ImClone. As ImClone s chief executive officer, he led ImClone through a significant turnaround, helping to restore the company s reputation and to secure FDA approval of ERBITUX (Cetuximab), a novel cancer treatment. As its chief financial officer, Mr. Lynch led negotiations to form the major partnership between ImClone and Bristol-Myers Squibb. Earlier in his career, he served in various financial positions at Bristol-Myers Squibb over a 15-year tenure. He served on the board of directors and the audit committee of U.S. Oncology, Inc. for five years until December 2010, when it was acquired by McKesson. Mr. Lynch received his B.A. in mathematics from Wesleyan University and his M.B.A. from

the Darden Graduate School of Business Administration at the University of Virginia. We believe that Mr. Lynch s experience as chief executive officer and chief financial officer of a public pharmaceutical company and as executive chairman and director for many other life science companies, qualify him to serve as a member of our board of directors.

John M. Maraganore, Ph.D. has served as a member of our board of directors since January 2012. Since December 2002, Dr. Maraganore has served as the chief executive officer and as a director of Alnylam Pharmaceuticals, Inc. From December 2002 to December 2007, Dr. Maraganore served as president of Alnylam. From April 2000 to December 2002, Dr. Maraganore served as senior vice president, strategic product development with Millennium Pharmaceuticals, Inc. Before Millennium, he served as director of molecular biology and director of market and business development at Biogen, Inc. (now Biogen Idec, Inc.). Prior to Biogen, Dr. Maraganore was a scientist at ZymoGenetics, Inc., and The Upjohn Company. Dr. Maraganore is also chairman of Regulus Therapeutics, Inc. and a director for Agios Pharmaceuticals and Tempero Pharmaceuticals. In addition, he is an advisor to Third Rock Ventures, L.P. He is also a member of the Immunology Advisory Council of Harvard Medical School and a member of the Biotechnology Industry Organization Board. Dr. Maraganore holds a B.A. in biological sciences from the University of Chicago and an M.S. and a Ph.D. in biochemistry and molecular biology from the University of Chicago. We believe that Dr. Maraganore s experience as chief executive officer and president of a public pharmaceutical company and chairman of another pharmaceutical company that just went public, qualify him to serve as a member of our board of directors.

Geert-Jan Mulder, M.D. has served as a member of our board of directors since May 2004. Dr. Mulder has been a general partner at Forbion Capital Partners since 2001. Prior to joining ABN AMRO Capital Life Sciences (now Forbion), he was clinical research manager of Byk Gulden (now Takeda) from 1999 to 2001 where his group was responsible for design and execution of early and late-stage clinical trials forming the basis for two global product registrations, Daxas and Alvesco in fields of COPD and asthma. For both products he was a member of the Global Medical Marketing group and supported the line extension program of Pantozol. From 1998 to 1999, he served as medical adviser in the field of arthritis and pain (COX-2 technology) and worked on the local and European positioning of Celebrex at Searle (now Pfizer). In addition to taking an active role in the Forbion Capital Partners investment process, Dr. Mulder serves on a number of boards and assists portfolio companies in their clinical development programs and overall strategy including Exosom Diagnostics, Inc., Pansgenetics B.V., Promedior, Inc. and Provesica, Ltd. He previously served on the board of Transave Inc. until its merger with Insmed in December 2010 and Acorda Therapeutics Inc. until its initial public offering in February 2006. Dr. Mulder is a certified Pharmaceutical Physician and earned both a masters in medicine and an M.D. from University of Utrecht. Before joining the pharmaceutical industry, he served as a resident in the field of obstetrics and gynecology. We believe that Dr. Mulder s experience in the venture capital industry, particularly with biotech and pharmaceutical companies, combined with his experience in clinical development, regulatory filings, Special Protocol Approval, orphan designations and dual experience in both the United States and Europe, qualify him to serve as a member of our board of directors. Dr. Mulder has indicated to us his intention to resign from our board of directors upon the consummation of this offering.

Dr. Axel Polack, has served as a member of our board of directors since May 2007. Dr. Polack joined TVM Capital in 2000 and is a general partner for life sciences in the firm s Munich office. He currently serves on the board of Noxxon Pharma AG, Invendo Medical, f-star and Probiodrug AG. Dr. Polack s main scientific fields of expertise are molecular and viral oncology, oncogene

activation, gene regulation and molecular immunology. He works intensively on the assessment of new investment opportunities in those areas, while also providing support to existing portfolio companies. Before joining TVM Capital, Dr. Polack was general manager of Innovative Technologies Neuherberg GmbH (now Ascenion). Ascenion acts as a marketing partner to research institutions of the Helmholtz-Gemeinschaft, such as GSF National Research Center for Environment and Health GmbH, which licenses patents and fosters start-up companies. In the eight years prior to joining Ascenion, Dr. Polack was the deputy head of the GSF Institute of Clinical Molecular Biology. He holds a M.D. from the University of Freiburg and a Second Thesis (postdoctoral lecture qualification Habilitation) in the field of virology. Dr. Polack s doctoral thesis was honored with the Goedecke Research prize for outstanding fundamental research in medicine. In 1995, he was appointed assistant professor/private lecturer by the Ludwig-Maximilian-University in Munich. Since 1984, he has co-authored more than 50 publications in peer review journals. We believe that Dr. Polack s experience in the venture capital industry, particularly with biotech and pharmaceutical companies, combined with his experience in virology, gene regulation, qualify him to serve as a member of our board of directors.

David P. Schenkein, M.D. has served as a member of our board of directors since April 2013. Since August 2009, Dr. Schenkein has served as the chief executive officer of Agios Pharmaceuticals. From April 2006 to July 2009, Dr. Schenkein served as senior vice president of oncology development and Genentech. Dr. Schenkein is also a director for Agios Pharmaceuticals, Foundation Medicine and Blueprint Medicine. Dr. Schenkein received his B.A. in chemistry from Wesleyan University and his M.D. from Upstate Medical School. We believe that Dr. Schenkein s experience as chief executive officer of Agios and his membership on the board of directors of a number of biopharmaceutical companies qualify him to serve as a member of our board of directors.

Robert I. Tepper, M.D. has served as a member of our board of directors since September 2010. Dr. Tepper is a distinguished scientist with over 25 years of experience building and operating leading R&D operations. Dr. Tepper co-founded Third Rock Ventures, L.P. in March 2007 and focuses on the formation, development and scientific strategy of the portfolio companies, as well as actively identifying and evaluating new investments. He also assumes active leadership roles in Third Rock s portfolio companies, functioning as chief scientific officer through the first 12-18 months post launch. Prior to joining Third Rock Ventures, L.P., Dr. Tepper served as president of research and development Millennium Pharmaceuticals, or Millenium, from 2003 to 2007 and was vital in its expansion from a drug discovery company to a fully integrated biopharmaceutical company. Before joining Millennium in 1994, he served as principal investigator in the laboratory of tumor biology at Massachusetts General Hospital Cancer Center. Dr. Tepper is also a founder and former member of the scientific advisory board of Cell Genesys/Abgenix. Dr. Tepper holds an A.B. in biochemistry from Princeton University and an M.D. from Harvard Medical School. Dr. Tepper serves as an adjunct faculty member at Harvard Medical School and Massachusetts General Hospital and is an advisory board member of several leading healthcare institutions, including the Partners HealthCare Center for Personalized Genetic Medicine, Harvard Medical School and Tufts Medical School. Dr. Tepper is a board member of Alcresta, Allena Pharmaceuticals, Cerulean Pharma Inc., Constellation Pharmaceuticals Inc. and Kala Pharmaceuticals, Inc. and is also on the board of overseers at Tufts University. We believe that Dr. Tepper s experience in the venture capital industry, particularly with biotech and pharmaceutical companies, combined with his experience building and operating research and development operations and as faculty and advisory board members of several healthcare institutions, qualify him to serve as a member of our board of directors.

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Board composition

We currently have nine directors, all of whom were elected pursuant to the terms of our voting agreement, which will terminate upon completion of this offering. Upon the termination of these provisions, we will not be bound by contractual obligations regarding the election of our directors.

Effective upon the closing of this offering, we will divide the terms of office of the directors into three classes:

Class I, whose term will expire at the annual meeting of stockholders to be held in 2014;

Class II, whose term will expire at the annual meeting of stockholders to be held in 2015; and

Class III, whose term will expire at the annual meeting of stockholders to be held in 2016.

Upon the closing of this offering, Class I shall consist of Dr. Gillis, Mr. Leschly and Dr. Polack, Class II shall consist of Mr. Lynch, Dr. Maraganore and Dr. Tepper and Class III shall consist of Dr. Dixon and Dr. Schenkein. Dr. Mulder, currently a member of our board of directors, has indicated to us his intention to resign from our board of directors upon the consummation of this offering. At each annual meeting of stockholders after the initial classification, the successors to directors whose terms will then expire shall serve from the time of election and qualification until the third annual meeting following election and until their successors are duly elected and qualified. A resolution of the board of directors may change the authorized number of directors. Any additional directorships resulting from an increase in the number of directors will be distributed among the three classes so that, as nearly as possible, each class will consist of one-third of the directors. This classification of the board of directors may have the effect of delaying or preventing changes in control or management of our company.

Following the closing of this offering, our nominating and corporate governance committee and board of directors may consider a broad range of factors relating to the qualifications and background of nominees, which may include diversity and is not limited to race, gender or national origin. We have no formal policy regarding board diversity. Our nominating and corporate governance committee s and board of directors priority in selecting board members is identification of persons who will further the interests of our company through his or her established record of professional accomplishment, the ability to contribute positively to the collaborative culture among board members, and professional and personal experiences and expertise relevant to our growth strategy.

Board committees

Our board of directors has established three standing committees: the audit committee, the compensation committee and the nominating and corporate governance committee.

Audit committee

Effective upon this offering, our audit committee will be composed of Dr. Dixon, Dr. Gillis and Mr. Lynch, with Dr. Gillis serving as chairman of the committee. Our board of directors has determined that each member of the audit committee meets the independence requirements of Rule 10A-3 under the Exchange Act and the applicable listing standards of Nasdaq. Our board of directors

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has determined that Mr. Lynch is an audit committee financial expert within the meaning of the SEC regulations and applicable listing standards of Nasdaq. The audit committee s responsibilities upon completion of this offering will include:

- appointing, approving the compensation of, and assessing the independence of our independent registered public accounting firm;
- approving audit and permissible non-audit services, and the terms of such services, to be provided by our independent registered public accounting firm;
- reviewing the internal audit plan with the independent registered public accounting firm and members of management responsible for preparing our financial statements;
- reviewing and discussing with management and the independent registered public accounting firm our annual and quarterly financial statements and related disclosures as well as critical accounting policies and practices used by us;
- reviewing the adequacy of our internal control over financial reporting;
- establishing policies and procedures for the receipt and retention of accounting-related complaints and concerns;
- recommending, based upon the audit committee s review and discussions with management and the independent registered public accounting firm, whether our audited financial statements shall be included in our Annual Report on Form 10-K;
- monitoring the integrity of our financial statements and our compliance with legal and regulatory requirements as they relate to our financial statements and accounting matters;
- preparing the audit committee report required by the rules of the Securities and Exchange Commission, or SEC, to be included in our annual proxy statement;
- reviewing all related party transactions for potential conflict of interest situations and approving all such transactions; and
- reviewing quarterly earnings releases and scripts.

Compensation committee

Effective upon this offering, our compensation committee will be composed of Mr. Lynch, Dr. Maraganore and Dr. Tepper, with Mr. Lynch serving as chairman of the committee. Our board of directors has determined each member of the compensation committee is independent as defined under the applicable listing standards of Nasdaq. The compensation committee s responsibilities upon completion of this offering will include:

- annually reviewing and approving corporate goals and objectives relevant to the compensation of our chief executive officer;

evaluating the performance of our chief executive officer in light of such corporate goals and objectives and determining the compensation of our chief executive officer;

reviewing and approving the compensation of our other executive officers;

appointing, compensating and overseeing the work of any compensation consultant, legal counsel or other advisor retained by the compensation committee;

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conduct the independence assessment outlined in Nasdaq rules with respect to any compensation consultant, legal counsel or other advisor retained by the compensation committee;

annually review and reassess the adequacy of the committee charter in its compliance with the listing requirements of Nasdaq;

reviewing and establishing our overall management compensation, philosophy and policy;

overseeing and administering our compensation and similar plans;

reviewing and approving our policies and procedures for the grant of equity-based awards;

reviewing and making recommendations to the board of directors with respect to director compensation;

reviewing and discussing with management the compensation discussion and analysis to be included in our annual proxy statement or Annual Report on Form 10-K; and

reviewing and discussing with the board of directors corporate succession plans for the chief executive officer and other key officers.

Nominating and corporate governance committee

Effective upon this offering, our nominating and corporate governance committee will be composed of Dr. Polack and Dr. Schenkein, with Dr. Polack serving as chairman of the committee. Our board of directors has determined that each member of the nominating and corporate governance committee is independent as defined under the applicable listing standards of Nasdaq. The nominating and corporate governance committee s responsibilities upon completion of this offering will include:

developing and recommending to the board of directors criteria for board and committee membership;

establishing procedures for identifying and evaluating board of director candidates, including nominees recommended by stockholders;

identifying individuals qualified to become members of the board of directors;

recommending to the board of directors the persons to be nominated for election as directors and to each of the board s committees;

developing and recommending to the board of directors a set of corporate governance guidelines; and

overseeing the evaluation of the board of directors and management.

Our board of directors may establish other committees from time to time.

Leadership structure and risk oversight

Our board of directors is currently chaired by Mr. Lynch. As a general policy, our board of directors believes that separation of the positions of chairman and chief executive officer reinforces the independence of the board of directors from management, creates an environment that

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encourages objective oversight of management s performance and enhances the effectiveness of the board of directors as a whole. As such, Mr. Leschly serves as our president and chief executive officer while Mr. Lynch serves as our chairman of the board of directors but is not an officer.

Our board of directors oversees the management of risks inherent in the operation of our business and the implementation of our business strategies. Our board of directors performs this oversight role by using several different levels of review. In connection with its reviews of the operations and corporate functions of our company, our board of directors addresses the primary risks associated with those operations and corporate functions. In addition, our board of directors reviews the risks associated with our company s business strategies periodically throughout the year as part of its consideration of undertaking any such business strategies.

Each of our board committees also oversees the management of our company s risk that falls within the committee s areas of responsibility. In performing this function, each committee has full access to management, as well as the ability to engage advisors. Our vice president of finance reports to the audit committee and is responsible for identifying, evaluating and implementing risk management controls and methodologies to address any identified risks. In connection with its risk management role, our audit committee meets privately with representatives from our independent registered public accounting firm and our chief financial officer. The audit committee oversees the operation of our risk management program, including the identification of the primary risks associated with our business and periodic updates to such risks, and reports to our board of directors regarding these activities.

Compensation committee interlocks and insider participation

None of the members of our compensation committee has at any time during the prior three years been one of our officers or employees. None of our executive officers currently serves, or in the past fiscal year has served, as a member of the board of directors or compensation committee of any entity that has one or more executive officers serving on our board of directors or compensation committee. For a description of transactions between us and members of our compensation committee and affiliates of such members, please see Certain relationships and related party transactions.

Code of business conduct and ethics

We have adopted a code of business conduct and ethics that applies to all of our employees, officers and directors, including those officers responsible for financial reporting. Upon the closing of this offering, our code of business conduct and ethics will be available on our website. We intend to disclose any amendments to the code, or any waivers of its requirements, on our website.

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Executive and director compensation

2012 summary compensation table

The following table sets forth the compensation earned during the fiscal year ended December 31, 2012 to our chief executive officer and our next two highest-paid executive officers as of December 31, 2012. We refer to these officers as our named executive officers.

Name and Principal Position	Year	Salary($)	Bonus($)(1)	Option awards($)(2)	Non-equity incentive plan compensation($)(3)	Total($)
Nick Leschly *President and Chief Executive Officer*	2012	346,085		130,738	124,200	601,023
Jeffrey T. Walsh *Chief Operating Officer*	2012	300,758			108,000	408,758
David M. Davidson, MD *Chief Medical Officer*	2012	260,456	45,000	223,857	82,156	611,469

(1) The amount reported consists of Dr. Davidson s signing bonus.

(2) The amounts reported in the Option awards column represent the grant date fair value of the stock options granted to our named executive officers during 2012 as computed in accordance with Accounting Standards Codification, or ASC, Topic 718, not including any estimates of forfeitures. The assumptions used in calculating the grant date fair value of the stock options reported in the Option awards column are set forth in Note 12 to our consolidated financial statements included elsewhere in this prospectus. Note that the amounts reported in this column reflect the accounting cost for these stock options, and do not correspond to the actual economic value that may be received by the named executive officers from the options.

(3) Amounts represent cash bonuses earned in 2012, and paid during 2013, based on achievement of performance goals and other factors deemed relevant by our board of directors. Our 2012 company objectives related primarily to clinical development and partnering achievements.

Narrative disclosure to summary compensation table

Employment arrangements with our named executive officers

Nick Leschly. We expect to enter into an amended and restated employment agreement, effective as of the closing of this offering, with Nick Leschly for the position of president and chief executive officer. Mr. Leschly currently receives a base salary of $390,000, which is subject to adjustment at the discretion of the board of directors. Mr. Leschly is also eligible for an annual performance bonus of up to 50% of his base salary, payable at the discretion of the board of directors. Mr. Leschly is eligible to participate in our employee benefit plans, subject to the terms of those plans.

Jeffrey T. Walsh. We expect to enter into an amended and restated employment agreement, effective as of the closing of this offering, with Jeffrey T. Walsh for the position of chief operating officer. Mr. Walsh currently receives a base salary of $320,000, which is subject to adjustment at the discretion of the board of directors. Mr. Walsh is also eligible for an annual performance bonus of up to 40% of his base salary, payable at the discretion of the board of directors. Mr. Walsh is eligible to participate in our employee benefit plans, subject to the terms of those plans.

David M. Davidson, M.D. We expect to enter into an amended and restated employment agreement, effective as of the closing of this offering, with David M. Davidson, M.D. for the position of chief medical officer. Dr. Davidson currently receives a base salary of $315,000, which is subject to adjustment at the discretion of the board of directors. Dr. Davidson is also eligible for an annual performance bonus of up to 35% of his base salary, payable at the discretion of the board of directors. Dr. Davidson is eligible to participate in our employee benefit plans, subject to

the terms of those plans.

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These employment agreements also contain provisions that provide for certain payments and benefits in the event of an involuntary termination of employment. In addition, the named executive officers may be entitled to accelerated vesting of their outstanding and unvested awards in certain circumstances. The information below describes certain compensation that may become due payable as a result of certain events. These payments and benefits are in addition to benefits available generally to salaried employees, including distributions under our Section 401(k) plan, accrued benefits under our health and welfare plans and arrangements and vacation pay or other accrued benefits under our medical and dental insurance plans, that are not generally described. Outstanding equity awards for the named executive officers as of December 31, 2012 are set forth under Outstanding equity awards at December 31, 2012.

Involuntary termination of employment

Pursuant to their employment agreements, each named executive officer is eligible to receive certain payments and benefits in the event his employment is terminated by us without cause (as defined in his offer letter) or in the event he terminates his employment with good reason (as defined in his offer letter). Upon the timely execution of a severance agreement, including a general release of claims, each named executive officer is eligible to receive the following payments and benefits:

- 12 months of base salary continuation; and
- if he elects to continue his group healthcare benefits, to the extent authorized by and consistent with COBRA, we will pay the named executive officer a monthly cash payment equal to the monthly employer contribution we would have made to provide him health insurance if he had remained employed by us until the earlier of (1) 12 months following the date of termination or (2) the end of the named executive officer s COBRA health continuation period.

Sale event

Pursuant to the employment agreements and the award agreements governing equity awards granted to the named executive officers prior to the date of the employment agreements, in the event of a sale event of the company (as defined in the 2010 Stock Option and Grant Plan), any such unvested stock options or other stock-based awards will immediately accelerate, vest and become fully exercisable or non-forfeitable as of the effective date of the sale event.

In addition, in the event that any of the named executive officers terminates his employment with us for good reason or his employment with us is terminated by us without cause, in each case within 12 months following a sale event (as defined in the 2013 Stock Option and Incentive Plan), he will be entitled to receive the following payments and benefits upon the timely execution of a severance agreement, including a general release of claims:

- a lump sum cash payment equal to one times (or one and a half times in the case of Mr. Leschly) the sum of (1) the named executive officer s then-current base salary (or base salary in effect immediately prior to the sale event, if higher) and (2) the named executive officer s target annual incentive compensation; and
- if he elects to continue his group healthcare benefits, to the extent authorized by and consistent with COBRA, we will pay the named executive officer a monthly cash payment

equal to the monthly employer contribution we would have made to provide him health insurance if he had remained employed by us until the earlier of (1) 12 months (or 18 months in the case of Mr. Leschly) following the date of termination or (2) the end of the named executive officer s COBRA health continuation period; and

all stock options and other stock-based awards granted to the named executive officer after the date of his employment agreement will become fully exercisable and non-forfeitable as of the date of the named executive officer s termination.

Definitions

For purposes of Mr. Leschly s employment agreement, cause means his:

commission of any felony or commission of any crime involving fraud, dishonesty or moral turpitude;

commission or attempted commission of, or participation in, a fraud or act of dishonesty against us;

material breach of any contract between Mr. Leschly and us or material breach of any legal duty Mr. Leschly owes to us;

conduct that constitutes insubordination, incompetence or neglect of duties; or

failure to perform the duties, functions and responsibilities of his position.

For purposes of each of the employment agreements with Mr. Walsh and Dr. Davidson, cause means the named executive officer s:

dishonest statements or acts with respect to us or any of our affiliates, or any of our current or prospective customers, suppliers, vendors or other third parties with which such entity does business;

commission of any felony or any misdemeanor involving moral turpitude, deceit, dishonesty or fraud;

failure to perform assigned duties to our reasonable satisfaction, which failure continues, in our reasonable judgment, after written notice to the named executive officer;

gross negligence, willful misconduct or insubordination with respect to us or any of our affiliates; or

violation of any provision of any agreement(s) between the named executive officer and us relating to noncompetition, nondisclosure and/or assignment of inventions.

For purposes of the each of the employment agreements with the named executive officers, good reason means:

a material diminution in the named executive officer s responsibilities, authority and function;

a material reduction in base salary other than pursuant to a salary reduction program affecting substantially all of our employees (or senior executives in the case of Dr. Davidson) that does not adversely affect the named executive officer to a greater

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extent than other similarly situated employees; provided, however, that any reduction in base salary that exceeds 10% of the named executive officer s then-current base salary shall constitute good reason;

a material change in the geographic location (of more than 30 miles in the case of Mr. Walsh) at which the named executive officer must regularly report to work or perform services, except for required travel on business (for Mr. Walsh and Dr. Davidson, to an extent substantially consistent with usual business travel obligations); and

a material breach by us of any provision of our equity incentive plans or award agreements thereunder or any other material agreement between the named executive officer and us concerning the terms of the named executive officer s employment, benefits or compensation.

In addition, under Mr. Leschly s employment agreement, good reason also includes:

an adverse change in the his job title or a change in reporting relationship as a result of which he no longer reports to our board of directors; and

removal from, or failure to be elected to, our board of directors.

Equity compensation

Outstanding equity awards at December 31, 2012

The following table sets forth information concerning the outstanding equity awards held by each of the named executive officers as of December 31, 2012.

	Option awards					Stock awards	
Name	Number of securities underlying unexercised options exercisable (#)	Number of securities underlying unexercised options unexercisable (#)	Number of securities underlying unexercised unearned options (#)	Option exercise price ($/share)	Option expiration date	Number of shares that have not vested (#)	Market value of shares that have not vested ($)(1)
Nick Leschly		1,750,000(2)		$ 0.11	6/4/2022		
	1,023,941	1,433,518(3)		0.11	7/13/2021		
						2,862,304(4)	$
Jeffrey T. Walsh			497,060(5)	0.11	7/13/2021		
	1,721,588	2,627,687(6)		0.11	7/13/2021		
David M. Davidson, M.D.		2,982,369(7)		0.11	4/13/2022		

(1) There was no public market for our common stock at December 31, 2012. We have estimated the market value of the unvested stock awards assuming an initial public offering price of $ per share, the midpoint of the price range set forth on the cover of this prospectus.

(2) Represents options to purchase shares of our common stock granted on June 4, 2012. The shares underlying these options vest as follows: 25% vest on May 1, 2013, with the remainder of the shares vesting in equal monthly installments over the following three years through May 1, 2016. Vesting of all unvested shares shall accelerate in connection with an acquisition event pursuant to the terms of the option agreement.

(3) Represents options to purchase shares of our common stock granted on July 13, 2011. The shares underlying these options vest as follows: 25% vest on April 15, 2012, with the remainder of the shares vesting in equal monthly installments over the following three years through April 15, 2015. Vesting of all unvested shares shall accelerate in connection with an acquisition event pursuant to the terms of the option agreement.

(4) Under the terms of Mr. Leschly s November 15, 2010 restricted stock agreement, the remaining unvested shares will vest in equal monthly installments through October 1, 2014. Vesting of all restricted shares shall accelerate in connection with an acquisition event pursuant to the terms of the restricted stock agreement.

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(5) Represents options to purchase shares of our common stock granted on July 13, 2011. The shares underlying these options vest as follows: 25% vest upon the one-year anniversary of the achievement of a performance-goal, with the remainder of the shares vesting in equal monthly installments over the following three years thereafter. Vesting of all unvested shares shall accelerate in connection with an acquisition event pursuant to the terms of the option agreement.

(6) Represents options to purchase shares of our common stock granted on July 13, 2011. The shares underlying these options vests as follows: 25% vest on May 16, 2012, with the remainder of the shares vesting in equal monthly installments over the following three years through May 16, 2015. Vesting of all unvested shares shall accelerate in connection with an acquisition event pursuant to the terms of the option agreement.

(7) Represents options to purchase shares of our common stock granted on April 13, 2012. The shares underlying these options vests as follows: 25% vest on February 13, 2013, with the remainder of the shares vesting in equal monthly installments over the following three years through February 13, 2016. Vesting of all unvested shares shall accelerate in connection with an acquisition event pursuant to the terms of the option agreement.

Director compensation

The following table sets forth a summary of the compensation we paid to our non-employee directors during 2012. Other than as set forth in the table and described more fully below, we did not pay any compensation, reimburse any expense of, make any equity awards or non-equity awards to, or pay any other compensation to any of the other non-employee members of our board of directors in 2012. Mr. Leschly, our president and chief executive officer, receives no compensation for his service as a director, and, consequently, is not included in this table. The compensation received by Mr. Leschly as an employee during 2012 is presented in 2012 summary compensation table above.

Name(1)	Fees earned or paid in cash($)	Option awards($)(2)	Total($)
Daniel S. Lynch	50,000		50,000
John M. Maraganore, Ph.D.	30,000	46,463	76,463

(1) As of December 31, 2012, Mr. Lynch and Dr. Maraganore held options to purchase 1,242,500 and 637,869 shares of common stock, respectively. None of the other non-employee members of our board of directors held options to purchase common stock or any other unvested share-based awards as of that date.

(2) The amounts reported in the Option Awards column represent the grant date fair value of the stock options granted to our non-employee directors during 2012 as computed in accordance with ASC Topic 718, not including any estimates of forfeitures. The assumptions used in calculating the grant date fair value of the stock options reported in the Option Awards column are set forth in Note 12 to our consolidated financial statements included elsewhere in this prospectus. Note that the amounts reported in this column reflect the accounting cost for these stock options, and do not correspond to the actual economic value that may be received by the non-employee directors from the options.

We have entered into offer letters with Mr. Lynch and Drs. Maraganore, Dixon and Schenkein regarding their service on our board of directors, which provide for annual cash retainers and reimbursement of expenses related to service as directors. These offer letters will terminate prior to the effectiveness of this registration statement, and each of these directors will be eligible to participate in the non-employee director compensation program described below following this offering. Each of these directors was granted an option to purchase shares of our common stock in connection with their appointment to the board of directors.

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Our board of directors has adopted a non-employee director compensation policy, effective as of the closing of this offering, that is designed to provide a total compensation package that enables us to attract and retain, on a long-term basis, high caliber non-employee directors. Under the policy, all non-employee directors will be paid cash compensation from and after the completion of this offering, as set forth below:

		Annual Retainer
Board of Directors:		
All non-employee members	$	35,000
Additional retainer for Non-Executive Chairman of the Board	$	25,000
Audit Committee:		
Chairman	$	15,000
Non-Chairman members	$	7,500
Compensation Committee:		
Chairman	$	10,000
Non-Chairman members	$	5,000
Nominating and Corporate Governance Committee:		
Chairman	$	7,000
Non-Chairman members	$	3,000

Under the non-employee director compensation policy, each person who is initially appointed or elected to the board of directors will be eligible for an option grant to purchase up to 260,000 shares of our common stock under our stock option plan on the date he or she first becomes a non-employee director, which will vest annually over a three-year period. In addition, on the date of the annual meeting of stockholders, each continuing non-employee director who has served on the board of directors for a minimum of six months will be eligible to receive an annual option grant to purchase up to 130,000 shares of our common stock, which will vest in full upon the earlier of the first anniversary of the date of grant or the date of the following annual meeting of stockholders. All of the foregoing options will be granted at fair market value on the date of grant.

Compensation risk assessment

We believe that our executive compensation program does not encourage excessive or unnecessary risk taking. This is primarily due to the fact that our compensation programs are designed to encourage our executive officers and other employees to remain focused on both short-term and long-term strategic goals, in particular in connection with our pay-for-performance compensation philosophy. As a result, we do not believe that our compensation programs are reasonably likely to have a material adverse effect on us.

Equity compensation plans and other benefit plans

2013 Stock Option and Incentive Plan

Our 2013 Stock Option and Incentive Plan, or the 2013 Plan, was adopted by our board of directors and approved by our stockholders in 2013 and will become effective immediately prior to this offering. The 2013 Plan will replace the 2010 Plan (as defined below).

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We have initially reserved shares of our 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 plan will automatically increase each January 1, beginning on January 1, 2014, by % of the outstanding number of shares of our common stock on the immediately preceding December 31 or such lesser number of shares as determined by our compensation committee. This number is subject to adjustment in the event of a stock split, stock dividend or other change in our capitalization.

The shares we issue under the 2013 Plan will be authorized but unissued shares or shares that we reacquire. The shares of common stock underlying any awards that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by us prior to vesting, satisfied without any issuance of stock, expire or are otherwise terminated (other than by exercise) under the 2013 Plan are added back to the shares of common stock available for issuance under the 2013 Plan.

Stock options and stock appreciation rights with respect to no more than shares of stock may be granted to any one individual in any one calendar year and the maximum performance-based award payable to any one individual under the 2013 Plan is shares of stock or $ in the case of cash-based awards. No more than shares may be issued as incentive stock options in any one calendar year period.

The 2013 Plan will be administered by our compensation committee. Our compensation committee has full power to select, from among the individuals eligible for awards, the individuals to whom awards will be granted, to make any combination of awards to participants, and to determine the specific terms and conditions of each award, subject to the provisions of the 2013 Plan. Persons eligible to participate in the 2013 Plan will be those full or part-time officers, employees, non-employee directors and other key persons (including consultants) as selected from time to time by our compensation committee in its discretion.

The 2013 Plan permits the granting of both (1) options to purchase common stock intended to qualify as incentive stock options under Section 422 of the Internal Revenue Code of 1986, as amended, or the Code, and (2) options that do not so qualify. The option exercise price of each option will be determined by our compensation committee but may not be less than 100% of the fair market value of our common stock on the date of grant. The term of each option will be fixed by our compensation committee and may not exceed ten years from the date of grant. Our compensation committee will determine at what time or times each option may be exercised.

Our compensation committee may award stock appreciation rights subject to such conditions and restrictions as it may determine. Stock appreciation rights entitle the recipient to shares of common stock, or cash, equal to the value of the appreciation in our stock price over the exercise price. The exercise price of each stock appreciation right may not be less than 100% of fair market value of the common stock on the date of grant.

Our compensation committee may award restricted shares of common stock and restricted stock units to participants subject to such conditions and restrictions as it may determine. These conditions and restrictions may include the achievement of certain performance goals and/or continued employment with us through a specified vesting period. Our compensation committee may also grant shares of common stock that are free from any restrictions under the 2013 Plan. Unrestricted stock may be granted to participants in recognition of past services or for other valid consideration and may be issued in lieu of cash compensation due to such participant.

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Our compensation committee may grant performance share awards to participants that entitle the recipient to receive share awards of common stock upon the achievement of certain performance goals and such other conditions as our compensation committee shall determine. Our compensation committee may grant dividend equivalent rights to participants that entitle the recipient to receive credits for dividends that would be paid if the recipient had held a specified number of shares of common stock.

Our compensation committee may grant cash bonuses under the 2013 Plan to participants, subject to the achievement of certain performance goals.

Our compensation committee may grant awards of restricted stock, restricted stock units, performance shares or cash-based awards under the 2013 Plan that are intended to qualify as performance-based compensation under Section 162(m) of the Code. Those awards would only vest or become payable upon the attainment of performance goals that are established by our compensation committee and related to one or more performance criteria. The performance criteria that could be used with respect to any such awards include: total shareholder return, earnings before interest, taxes, depreciation and amortization, net income (loss) (either before or after interest, taxes, depreciation and/or amortization), changes in the market price of our common stock, economic value-added, funds from operations or similar measure, sales or revenue, development, clinical or regulatory milestones, acquisitions or strategic transactions, operating income (loss), cash flow (including, but not limited to, operating cash flow and free cash flow), return on capital, assets, equity, or investment, return on sales, gross or net profit levels, productivity, expense, margins, operating efficiency, customer satisfaction, working capital, earnings (loss) per share of stock, sales or market shares and number of customers, any of which may be measured either in absolute terms or as compared to any incremental increase or as compared to results of a peer group. From and after the time that we become subject to Section 162(m) of the Code, the maximum award that is intended to qualify as performance-based compensation under Section 162(m) of the Code that may be made to any one employee during any one calendar year period is shares of common stock with respect to a stock-based award and $ with respect to a cash-based award.

The 2013 Plan provides that upon the effectiveness of a sale event, as defined in the 2013 Plan, in the event that all awards are not assumed or continued or substituted by the successor entity, all options and stock appreciation rights that are not exercisable immediately prior to the effective time of the sale event shall become fully exercisable as of the effective time of the sale event, all other awards with time-based vesting, conditions or restrictions, shall become fully vested and nonforfeitable as of the effective time of the sale event and all awards with conditions and restrictions relating to the attainment of performance goals may become vested and nonforfeitable in the discretion of the compensation committee and all awards granted under the 2013 Plan shall terminate. In addition, in connection with the termination of the 2013 Plan upon a sale event, we may make or provide for a cash payment to participants holding options and stock appreciation rights equal to the difference between the per share cash consideration payable to stockholders in the sale event and the exercise price of the options or stock appreciation rights.

Our board of directors may amend or discontinue the 2013 Plan and our compensation committee may amend or cancel outstanding awards for purposes of satisfying changes in law or any other lawful purpose, but no such action may adversely affect rights under an award without the holder s consent. Certain amendments to the 2013 Plan require the approval of our stockholders.

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No awards may be granted under the 2013 Plan after the date that is ten years from the date of stockholder approval of the 2013 Plan. No awards under the 2013 Plan have been made prior to the date hereof.

2013 Employee Stock Purchase Plan

Our 2013 Employee Stock Purchase Plan was adopted by our board of directors and approved by our stockholders in 2013 and will become effective upon closing of this offering. Our 2013 Employee Stock Purchase Plan authorizes the initial issuance of up to a total of shares of our common stock to participating employees.

All employees who have been employed by us or our designated subsidiaries for at least and whose customary employment is for are eligible to participate in our 2013 Employee Stock Purchase Plan. Any employee who owns, or would own upon such purchase under our 2013 Employee Stock Purchase Plan, 5% or more of the voting power or value of our stock is not eligible to purchase shares under our 2013 Employee Stock Purchase Plan.

We may make one or more offerings to our employees to purchase stock under our 2013 Employee Stock Purchase Plan. Unless otherwise determined by the administrator of our 2013 Employee Stock Purchase Plan, the first offering will begin on of the year designated by the administrator and end on the following . Subsequent offerings will begin on the first business day occurring on or after each and and will continue for periods, referred to as offering periods. The administrator may designate different offering periods in its discretion but no offering shall exceed six months in duration or overlap with another offering.

Each employee who is a participant in our 2013 Employee Stock Purchase Plan may purchase shares by authorizing payroll deductions of up to % of his or her eligible compensation during an offering period. Unless the participating employee has previously withdrawn from the offering, his or her accumulated payroll deductions will be used to purchase common stock on the last business day of the offering period at a price equal to % of the fair market value of the common stock on or the last business day of the offering period, whichever is lower, provided that no more than shares of common stock or such other maximum number established by the compensation committee may be purchased by any one employee during each offering period. Under applicable tax rules, an employee may purchase no more than $25,000 worth of common stock, valued at the start of the purchase period, under our 2013 Employee Stock Purchase Plan in any calendar year.

The accumulated payroll deductions of any employee who is not a participant on the last day of an offering period will be refunded. An employee s rights under our 2013 Employee Stock Purchase Plan terminate upon voluntary withdrawal from the plan or when the employee ceases employment for any reason.

Our 2013 Employee Stock Purchase Plan may be terminated or amended by our board of directors at any time. Amendments that increase the number of shares of our common stock authorized under our 2013 Employee Stock Purchase Plan and certain other amendments require the approval of our stockholders.

2010 Stock Option and Grant Plan

Our 2010 Stock Option and Grant Plan, or the 2010 Plan, was approved by our board of directors on September 15, 2010 and was subsequently approved by our stockholders on October 4, 2010. The

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2010 Plan was most recently amended in January 2013. Under the 2010 Plan, as of January 16, 2013, we have reserved for issuance an aggregate of (i) 81,953,382 shares of our common stock plus (ii) the number of shares of common stock returned to the 2002 Plan, as defined below, after January 16, 2013. The number of shares of common stock reserved for issuance is subject to adjustment in the event of a stock split, stock dividend or other change in our capitalization.

The shares we issue under the 2010 Plan will be authorized but unissued shares or shares we reacquire. The shares of common stock underlying any awards that are forfeited, canceled, repurchased, expire or are otherwise terminated (other than by exercise) under the 2010 Plan are added to the shares of common stock available for issuance under the 2010 Plan. Upon this offering, such shares will be added to the shares of common stock available for issuance under the 2013 Plan.

Our board of directors has acted as administrator of the 2010 Plan. The administrator has full power to select, from among the individuals eligible for awards, the individuals to whom awards will be granted, and to determine the specific terms and conditions of each award, subject to the provisions of the 2010 Plan. Persons eligible to participate in the 2010 Plan are those full or part-time officers, employees, directors, consultants and other key persons (including prospective employees, but conditioned upon their employment) of us and our subsidiaries as selected from time to time by the administrator in its discretion.

The 2010 Plan permits the granting of (1) options to purchase common stock intended to qualify as incentive stock options under Section 422 of the Code and (2) options that do not so qualify. The option exercise price of each option will be determined by the administrator but may not be less than 100% of the fair market value of the common stock on the date of grant. The term of each option will be fixed by the administrator and may not exceed ten years from the date of grant. The administrator will determine at what time or times each option may be exercised. In addition, the 2010 Plan permits the granting of restricted shares of common stock, restricted stock units and unrestricted stock.

The 2010 Plan provides that upon the occurrence of a sale event as defined in the 2010 Plan, all outstanding stock options will terminate at the effective time of such sale event, unless the parties to the sale event agree that such awards will be assumed or continued by the successor entity. In the event of a termination of the 2010 Plan and all options issued thereunder in connection with a sale event, the optionees will be provided an opportunity to exercise their options prior to the completion of the sale event. In the case of a sale event in which our stockholders will receive cash consideration, the administrator has the right to provide for cash payment to holders of vested options in an amount equal to the difference between the per share cash consideration and the exercise price of such options. Restricted stock and restricted stock units will be forfeited immediately prior to the effective time of a sale event unless such awards are assumed or continued by the successor entity. In the event that the shares of restricted stock are forfeited in connection with a sale event, such shares of restricted stock shall be repurchased at a price per share equal to the lower of the original per share purchase price and the fair market value of such shares. The administrator has the right to provide for cash payment to holders of restricted stock or restricted stock units in an amount equal to the per share cash consideration in the sale event.

No awards may be granted under the 2010 Plan after the date that is ten years from the date the 2010 Plan was adopted by the board of directors. Our board of directors has determined not to make any further awards under the 2010 Plan following the closing of this offering.

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2002 Employee, Director and Consultant Plan

Our Second Amended and Restated 2002 Employee, Director and Consultant Stock Plan, or the 2002 Plan, was approved by our board of directors and our stockholders on June 2, 2004. Our board of directors has not granted any awards under our 2002 Plan since it terminated on October 4, 2010 and does not plan to grant any further awards under our 2002 Plan. As of December 31, 2012, there were options to purchase 5,420,099 shares of common stock outstanding under the 2002 Plan.

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 are added to the shares of common stock available for issuance under the 2010 Plan. Upon this offering, such shares will be added to the shares of common stock available for issuance under the 2013 Plan.

The 2002 Plan provides that upon the occurrence of a corporate transaction as defined in the 2002 Plan, the parties to such corporate transaction may provide that (i) the options will be assumed or continued by the successor entity, (ii) optionees will be provided an opportunity to exercise their options prior to the completion of the corporate transaction, or (iii) vested options will be terminated in exchange for a cash payment equal to the difference between the fair market value of the shares subject to the options and the exercise price.

Executive Cash Incentive Bonus Plan

Our board of directors has adopted the Executive Cash Incentive Bonus Plan, or the Bonus Plan, which is effective as of the closing of this offering. The Bonus Plan provides for cash bonus payments based upon the attainment of performance targets established by our compensation committee. The payment targets will be related to corporate, financial and operational measures or objectives, or Corporate Performance Goals, as well as individual performance objectives.

Our compensation committee may select Corporate Performance Goals from among the following: achievement of specified research and development, publication, clinical and/or regulatory milestones; cash flow (including, but not limited to, operating cash flow and free cash flow); sales or revenue; corporate revenue; earnings before interest, taxes, depreciation and amortization; net income (loss) (either before or after interest, taxes, depreciation and/or amortization); changes in the market price of our common stock; economic value-added; funds from operations or similar measure; acquisitions or strategic transactions; operating income (loss); return on capital, assets, equity, or investment; stockholder returns; return on sales; gross or net profit levels; productivity; expense efficiency; margins; operating efficiency; customer satisfaction; working capital; earnings (loss) per share of our common stock; bookings, new bookings or renewals; sales or market shares; number of customers; number of new customers or customer references; operating income and/or net annual recurring revenue, any of which may be measured in absolute terms, as compared to any incremental increase, in terms of growth, as compared to results of a peer group, against the market as a whole, compared to applicable market indices and/or measured on a pre-tax or post-tax basis.

Each executive officer who is selected to participate in the Bonus Plan will have a target bonus opportunity set for each performance period. The bonus formulas will be adopted in each performance period by the compensation committee and communicated to each executive. The Corporate Performance Goals will be measured at the end of each performance period after our financial reports have been published or such other appropriate time as the compensation

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committee determines. If the Corporate Performance Goals and individual performance objectives are met, payments will be made as soon as practicable following the end of each performance period. Subject to the rights contained in any agreement between the executive officer and the company, an executive officer must be employed by the company on the bonus payment date to be eligible to receive a bonus payment. The Bonus Plan also permits the compensation committee to approve additional bonuses to executive officers in its sole discretion.

401(k) plan

We maintain a 401(k) plan for employees. The 401(k) plan is intended to qualify under Section 401(k) of the Code, so that contributions to the 401(k) plan by employees or by us, and the investment earnings thereon, are not taxable to the employees until withdrawn from the 401(k) plan, and so that contributions by us, if any, will be deductible by us when made. Under the 401(k) plan, employees may elect to reduce their current compensation by up to the statutorily prescribed annual limit and to have the amount of such reduction contributed to the 401(k) plan. The 401(k) plan permits us to make contributions up to the limits allowed by law on behalf of all eligible employees. Historically, we have not made any matching contributions to the 401(k) plan.

Rule 10b5-1 sales plans

Our directors and executive officers may adopt written plans, known as Rule 10b5-1 plans, in which they will contract with a broker to buy or sell shares of our common stock on a periodic basis. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the director or officer when entering into the plan, without further direction from the director or officer. The director or officer may amend or terminate the plan in limited circumstances. Our directors and executive officers may also buy or sell additional shares of our common stock outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

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Certain relationships and related party transactions

The following is a description of transactions since January 1, 2010 to which we have been a party, in which the amount involved exceeds $120,000, and in which any of our directors, executive officers or holders of more than 5% of our capital stock, or an affiliate or immediate family member thereof, had or will have a direct or indirect material interest. We believe the terms obtained or consideration that we paid or received, as applicable, in connection with the transactions described below were comparable to terms available or the amounts that would be paid or received, as applicable, from unaffiliated third parties.

Sales and purchases of securities

Series B financing

In March 2010, we issued an aggregate of 61,555,660 shares of our Series B Preferred Stock for aggregate consideration of $16.8 million in cash and $3.3 million in converted bridge notes to five investors. In April 2011, we issued, pursuant to a second tranche closing, an aggregate of 53,648,066 shares of our Series B Preferred Stock for aggregate consideration of $17.5 million to the same five investors. The table below sets forth the aggregate number of shares of Series B Preferred Stock sold to our directors, executive officers or holders of more than 5% of our capital stock, or an affiliate or immediate family member thereof:

Name	Shares	Aggregate purchase price
Third Rock Ventures, L.P.	64,377,682	$ 21,000,000
TVM V Life Science Ventures GmbH & Co. KG	17,749,014	$ 5,789,728
Cooperative AAC LS U.A.	10,649,408	$ 3,473,837

In May 2007, December 2007, May 2008, August 2008, December 2008, April 2009, July 2009, October 2009 and December 2009, we issued warrants to purchase 1,133,100, 472,124, 472,124, 472,124, 472,124, 321,044, 321,044, 283,274, and 574,800 shares, respectively, of either (i) our Series A-1 Preferred Stock or (ii) such preferred stock that we may issue in a subsequent qualified financing. In March 2010, in connection with the Series B Preferred Stock financing, the 2007, 2008 and the April, July and October 2009 warrants were amended to provide that such warrants would be exercisable only for shares of our Series A-1 Preferred Stock at a per share price of $0.6619 and the December 2009 warrants were amended to provide that such warrants would be exercisable only for shares of our Series B Preferred Stock at a per share price of $0.3262. The table below set forth the number and class of shares issuable pursuant to warrants amended in March 2010 held by our directors, executive officers or holders of more than 5% of our capital stock, or an affiliate or immediate family member thereof:

Name	Warrants to purchase shares of Series A-1 preferred stock	Warrants to purchase shares of Series B preferred stock
TVM V Life Science Ventures GmbH & Co. KG	3,075,111	287,400
Cooperative AAC LS U.A.	1,656,206	172,440

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Series C financing

In April 2011, we issued an aggregate of 39,942,483 shares of our Series C Preferred Stock for aggregate consideration of $15.0 million to five investors. The table below sets forth the number of shares of Series C Preferred Stock sold to our directors, executive officers or holders of more than 5% of our capital stock, or an affiliate or immediate family member thereof:

Name	Shares	Aggregate purchase price
ARCH Venture Fund VII, L.P.	19,971,242	$ 7,500,000
Third Rock Ventures, L.P.	14,379,294	$ 5,400,000
TVM V Life Science Ventures GmbH & Co. KG	3,994,248	$ 1,500,000
Cooperative AAC LS U.A.	1,331,416	$ 500,000

Series D financing

In July 2012, we issued an aggregate of 120,409,385 shares of our Series D Preferred Stock for aggregate consideration of $60.0 million to 17 investors. The table below sets forth the number of shares of Series D Preferred Stock sold to our directors, executive officers or holders of more than 5% of our capital stock, or an affiliate or immediate family member thereof:

Name	Shares	Aggregate purchase price
Entities Affiliated with Fidelity Investors	37,728,275	$ 18,800,000
Entities Affiliated with Capital Research and Management Company	29,500,300	$ 14,700,000
ARCH Venture Fund VII, L.P.	14,047,762	$ 7,000,000
Third Rock Ventures, L.P.	11,037,527	$ 5,500,000
TVM V Life Science Ventures GmbH & Co. KG	3,010,234	$ 1,500,000
Cooperative AAC LS U.A.	1,003,411	$ 500,000

Consulting services provided by Third Rock Ventures, LLC

During the fiscal years ended December 31, 2010, 2011 and 2012, we incurred consulting fees to Third Rock Ventures, LLC in the amount of $0.8, $0.4 and $0.1 million, respectively. Third Rock Ventures, LLC is a management company that is party to a services agreement with Third Rock Ventures, L.P., the beneficial owner of more than five percent of our voting securities. Robert I. Tepper, M.D., one of our directors, is a managing member of TRV GP, LLC, which is the general partner of Third Rock Ventures GP, L.P., the general partner of Third Rock Ventures, L.P. and a managing member of Third Rock Ventures, LLC. These consulting fees were paid to Third Rock Ventures, LLC in consideration of certain strategic and business operations consulting services provided to us during this period by Third Rock Ventures, LLC by individuals other than Dr. Tepper. None of these consulting fees were paid directly or indirectly to Dr. Tepper. The consulting fees paid to Third Rock Ventures, LLC did not exceed five percent of the consolidated gross revenues of Third Rock Ventures, LLC during any of these fiscal years. We are not currently party to a consulting agreement with Third Rock Ventures, LLC and we do not expect to engage Third Rock Ventures, LLC for consulting services on a going forward basis.

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Director and executive officer compensation

Please see Executive and director compensation Director compensation for a discussion of options granted to our non-employee directors. Please see Executive and director compensation Equity compensation for additional information regarding compensation of executive officers.

Employment agreements

We have entered into employment agreements with our executive officers. For more information regarding these agreements, see Executive and director compensation Employment agreements with our named executive officers.

Indemnification agreements and directors and officers liability insurance

We have entered into indemnification agreements with each of our executive officers and directors.

Registration rights agreements

We and certain holders of our preferred stock have entered into an investor rights agreement pursuant to which these stockholders will have, among other things, registration rights under the Securities Act of 1933, as amended, with respect to common stock that they will hold following this offering. Upon the closing of this offering, all outstanding shares of our preferred stock will be converted into common stock. See Description of capital stock Registration rights for a further description of the terms of these agreements.

Procedures for related party transactions

We have adopted a related person transaction approval policy that will govern the review of related person transactions following the closing of this offering. Pursuant to this policy, if we want to enter into a transaction with a related person or an affiliate of a related person, our chief operating officer will review the proposed transaction to determine, based on applicable Nasdaq and Securities and Exchange Commission rules, if such transaction requires pre-approval by the audit committee and/or board of directors. If pre-approval is required, such matters will be reviewed at the next regular or special audit committee and/or board of directors meeting. We may not enter into a related person transaction unless our chief operating officer has either specifically confirmed in writing that no further reviews are necessary or has confirmed that all requisite corporate reviews have been obtained.

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Principal stockholders

The following table sets forth information relating to the beneficial ownership of our common stock as of March 31, 2013, by:

- each person, or group of affiliated persons, known by us to beneficially own more than 5% of our outstanding shares of common stock;
- each of our directors;
- each of our named executive officers; and
- all directors and executive officers as a group.

The number of shares beneficially owned by each entity, person, director or executive officer is determined in accordance with the rules of the Securities and Exchange Commission, and the information is not necessarily indicative of beneficial ownership for any other purpose. Under such rules, beneficial ownership includes any shares over which the individual has sole or shared voting power or investment power as well as any shares that the individual has the right to acquire within 60 days of March 31, 2013 through the exercise of any stock option, warrants or other rights. Except as otherwise indicated, and subject to applicable community property laws, the persons named in the table have sole voting and investment power with respect to all shares of common stock held by that person.

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The percentage of shares beneficially owned is computed on the basis of 319,946,737 shares of our common stock outstanding as of March 31, 2013, which reflects the assumed conversion of all of our outstanding shares of preferred stock into an aggregate of 310,841,204 shares of common stock. Shares of our common stock that a person has the right to acquire within 60 days of March 31, 2013 are deemed outstanding for purposes of computing the percentage ownership of the person holding such rights, but are not deemed outstanding for purposes of computing the percentage ownership of any other person, except with respect to the percentage ownership of all directors and executive officers as a group. Unless otherwise indicated below, the address for each beneficial owner listed is c/o bluebird bio, Inc., 840 Memorial Drive, 4th Floor, Cambridge, MA 02139.

Name and address of beneficial owner	Number of shares beneficially owned	Percentage of shares beneficially owned Before offering	After offering
5% or greater stockholders:			
Third Rock Ventures, L.P.(1) 29 Newbury Street Boston, MA 02116	89,794,503	28.1%	
TVM V Life Science Ventures GmbH & Co. KG(2) Maximilianstrasse 35 Entrance C 80539 Munich, Germany	46,120,958	14.3%	
Entities affiliated with Fidelity Investments(3) 82 Devonshire St. Boston, MA 02109	37,728,275	11.8%	
ARCH Venture Fund VII, L.P.(4) 8725 West Higgins Road Suite 290 Chicago, IL 60631	34,019,004	10.6%	
Entities affiliated with Capital Research and Management Company(5) 333 S. Hope Street, 55th Floor Los Angeles, CA 90071	29,500,300	9.2%	
Coöperative AAC LS U.A. (Forbion)(6) PO Box 5187 1410 AD Naarden The Netherlands	23,737,882	7.4%	

Directors and named executive officers:		
Nick Leschly(7)	7,962,439	2.5%
Robert I. Tepper, M.D.(8)	89,794,503	28.1%
Dr. Axel Polack(9)	46,120,958	14.3%
Steven Gillis, Ph.D.(10)	34,019,004	10.6%
Geert-Jan Mulder, M.D.(11)	23,737,882	7.4%
Daniel S. Lynch(12)	647,135	*
John M. Maraganore, Ph.D.(13)	224,289	*
Wendy L. Dixon, Ph.D.		
David P. Schenkein, M.D.		
Jeffrey T. Walsh(14)	2,174,637	*
David Davidson, M.D.(15)	931,990	*
All executive officers and directors as a group (11 persons)(16)	208,553,356	62.5%

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* Represents beneficial ownership of less than one percent of our outstanding common stock.

(1) Consists of (i) 64,377,682 shares of common stock underlying shares of Series B Convertible Preferred Stock, or Series B Stock, (ii) 14,379,294 shares of common stock underlying shares of Series C Convertible Preferred Stock, or Series C Stock, and (iii) 11,037,527 shares of common stock underlying shares of Series D Convertible Preferred Stock, or Series D Stock. All shares are held directly by Third Rock Ventures, L.P. (TRV LP). Each of Third Rock Ventures GP, LP (TRV GP), the general partner of TRV LP, and Third Rock Ventures GP, LLC (TRV LLC), the general partner of TRV GP, may be deemed to have voting and dispositive power over the shares held by TRV LP. Investment decisions with respect to the shares held by TRV LP are made by an investment committee at TRV GP comprised of Mark Levin, Kevin Starr, Bob Tepper, Neil Exter, Kevin Gillis, Lou Tartaglia, Craig Muir, Cary Pfeffer, Alexis Borisy and Craig Greaves. No stockholder, director, officer, manager, member or employee of TRV GP or TRV LLC has beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act) of any shares held by TRV LP.

(2) Consists of (i) 6,169,117 shares of common stock underlying shares of Series A-1 Convertible Preferred Stock, or Series A-1 Stock, and 3,075,111 shares of common stock underlying warrants to purchase Series A-1 Stock that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date, (ii) 11,835,834 shares of common stock underlying shares of Series A-2 Convertible Preferred Stock, or Series A-2 Stock, (iii) 17,749,014 shares of common stock underlying shares of Series B Stock and 287,400 shares of common stock underlying warrants to purchase Series B Stock that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date, (iv) 3,994,248 shares of common stock underlying shares of Series C Stock and (iv) 3,010,234 shares of common stock underlying shares of Series D Stock. All shares are held directly by TVM V Life Science Ventures GmbH & Co. KG. (TVM LSV V). Its general partner TVM Capital, or TVM, and its authorized officers Axel Polack, Helmut Schuehsler, Alexandra Goll, Hubert Birner and Stefan Fischer may be deemed to share voting and dispositive power over the shares held by TVM LSV V. No stockholder, director, officer, manager, member or employee of TVM and no director, officer, manager, member or employee of TVM LSV V has beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act) of any shares held by TVM LSV V.

(3) Consists of (i) 19,295,922 shares of common stock underlying shares of Series D Stock held by Mag & Co. f/b/o Fidelity Contrafund: Fidelity Contrafund, (ii) 4,658,909 shares of common stock underlying shares of Series D Stock held by Mag & Co. f/b/o Fidelity Contrafund: Fidelity Advisor New Insights Fund, (iii) 9,767,944 shares of common stock underlying shares of Series D Stock held by Ball & Co. f/b/o Fidelity Mt. Vernon Street Trust: Fidelity Growth Company Fund, (iv) 535,716 shares of common stock underlying shares of Series D Stock held by Mag & Co. f/b/o Fidelity Select Portfolios: Biotechnology Portfolio, (v) 35,360 shares of common stock underlying shares of Series D Stock held by Bangle & Co f/b/o Fidelity Advisor Series VII: Fidelity Advisor Biotechnology Fund and (vi) 3,434,424 shares of common stock underlying shares of Series D Stock held by Sailboat & Co. f/b/o Fidelity Magellan Fund: Fidelity Magellan Fund. Each of these entities is a registered investment fund (each, a Fund) advised by Fidelity Management & Research Company (FMR Co.), a registered investment adviser under the Investment Advisers Act of 1940, as amended. The address of FMR Co., a wholly-owned subsidiary of FMR LLC and an investment adviser registered under Section 203 of the Investment Advisers Act of 1940 is 82 Devonshire Street, Boston, Massachusetts 02109. FMR LLC, through its control of FMR Co., Edward C. Johnson 3d, as Chairman of FMR LLC, and each Fund has power to dispose of the securities owned by such Fund. Neither FMR LLC nor Edward C. Johnson 3d has sole power to vote or direct the voting of the shares owned directly by each Fund, which power resides with each Fund s Board of Trustees.

(4) Consists of (i) 19,971,242 shares of common stock underlying shares of Series C Stock and (ii) 14,047,762 shares of common stock underlying shares of Series D Stock. All shares are held directly by ARCH Venture Fund VII, L.P. (ARCH VII). ARCH Venture Partners VII, L.P. (the GPLP), as the sole general partner of ARCH VII, may be deemed to beneficially own certain of the shares held of record by ARCH VII. The GPLP disclaims beneficial ownership of all shares held of record by ARCH VII in which the GPLP does not have an actual pecuniary interest. ARCH Venture Partners VII, LLC (the GPLLC), as the sole general partner of the GPLP, may be deemed to beneficially own certain of the shares held of record by ARCH VII. The GPLLC disclaims beneficial ownership of all shares held of record by ARCH VII in which it does not have an actual pecuniary interest. Keith Crandell, Clinton Bybee and Robert Nelsen are the managing directors of the GPLLC, and may be deemed to share voting and dispositive power over the shares held of record by ARCH VII. The managing directors disclaim beneficial ownership of all shares held of record by ARCH VII in which they do not have an actual pecuniary interest. Steven Gillis, one of our directors, owns an interest in GPLP. Mr. Gillis does not have voting or disposition authority of the shares held by ARCH VII.

(5) Consists of (i) 22,374,386 shares of common stock underlying shares of Series D Stock held by Clipperbay & Co. HG22 as nominee for SMALLCAP World Fund, Inc. and (ii) 7,125,914 shares of common stock underlying shares of Series D Stock held by Piping & Co. HG19 as nominee for American Funds Insurance Series Global Small Capitalization Fund. Capital Research and Management Company serves as the investment adviser for SMALLCAP World Fund, Inc. and American Funds Insurance Series Global Small Capitalization Fund. Capital Research and Management Company or its affiliates has voting and dispositive power of all of the shares held by these funds and may be deemed to be the beneficial owner for purposes of reporting requirements of the Exchange Act. Capital Research and Management Company, however, expressly disclaims that it is, in fact, the beneficial owner of such securities. Capital Research and Management Company is an investment adviser registered under the Investment Advisers Act of 1940.

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(6) Consists of (i) 2,643,906 shares of common stock underlying shares of Series A-1 Stock and 1,656,206 shares of common stock underlying warrants to purchase Series A-1 Stock that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date, (ii) 6,281,095 shares of common stock underlying shares of Series A-2 Stock, (iii) 10,649,408 shares of common stock underlying shares of Series B Stock and 172,440 shares of common stock underlying warrants to purchase Series B Stock that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date, (iv) 1,003,411 shares of common stock underlying shares of Series C Stock and (iv) 3,010,234 shares of common stock underlying shares of Series D Stock. All shares are held by Coöperative AAC LS U.A., or Coöperative. Forbion 1 Management B.V., or Forbion, the director of Coöperative, may be deemed to have voting and dispositive power over the shares held by Coöperative. Investment decisions with respect to the shares held by Coöperative can made by any two of the six duly authorized representatives of Coöperative, which comprise directors L.P.A. Bergstein, M.A. van Osch, H.A. Slootweg and proxy holders S.J.H. van Deventer, G.J. Mulder and C. Takke. No stockholder, director, officer, manager, member or employee of Coöperative or Forbion has beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act) of any shares held by Coöperative.

(7) Includes 1,717,426 shares of common stock underlying options that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date.

(8) Consists of 89,794,503 shares of common stock into which the shares of preferred stock beneficially owned by Third Rock Ventures, L.P. are convertible. Dr. Tepper is a partner of Third Rock Ventures, L.P. and may be deemed to have voting and investment power over the shares held by Third Rock Ventures, L.P. Dr. Tepper disclaims beneficial ownership with respect to any such shares, except to the extent of his pecuniary interest therein, if any.

(9) Consists of (i) 42,758,447 shares of common stock into which the shares of preferred stock beneficially owned by TVM V Life Science Ventures GmbH & Co. KG are convertible and (ii) 3,362,511 shares of common stock underlying preferred stock warrants that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date. Dr. Polack is a managing limited partner of TVM V Life Science Ventures GmbH & Co. KG and may be deemed to have voting and investment power, jointly not solely, over the shares held by TVM V Life Science Ventures GmbH & Co. KG. Dr. Polack disclaims beneficial ownership with respect to any such shares, except to the extent of his pecuniary interest therein, if any.

(10) Consists of 34,019,004 shares of common stock into which the shares of preferred stock beneficially owned by ARCH Venture Fund II, L.P. are convertible. ARCH Venture Fund II, L.P. is an affiliated fund of ARCH Venture Partners. Dr. Gillis is a managing director with ARCH Venture Partners and may be deemed to have voting and investment power over the shares held by ARCH Venture Fund II, L.P. Dr. Gillis disclaims beneficial ownership with respect to any such shares, except to the extent of his pecuniary interest therein, if any.

(11) Consists of (i) 23,737,882 shares of common stock into which the shares of preferred stock beneficially owned by Coöperative AAC LS U.A. are convertible and (ii) 1,828,646 shares of common stock underlying preferred stock warrants that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date. Dr. Mulder is a general partner of Coöperative AAC LS U.A. and may be deemed to have voting and investment power over the shares held by Forbion Capital Partners. Dr. Mulder disclaims beneficial ownership with respect to any such shares, except to the extent of his pecuniary interest therein, if any.

(12) Consists of 647,135 shares of common stock underlying options that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date.

(13) Consists of 224,289 shares of common stock underlying options that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date.

(14) Consists of 2,174,637 shares of common stock underlying options that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date.

(15) Consists of 931,990 shares of common stock underlying options that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date.

(16)

Includes (i) 5,191,157 shares of common stock underlying preferred stock warrants that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date and (ii) 8,635,997 shares of common stock underlying options that are exercisable as of March 31, 2013 or will become exercisable within 60 days after such date.

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Description of capital stock

General

Upon completion of this offering, our authorized capital stock will consist of shares of common stock, par value $0.01 per share, and shares of preferred stock, par value $0.01 per share. The following description of our capital stock is intended as a summary only and is qualified in its entirety by reference to our amended and restated certificate of incorporation, or our certificate of incorporation, and amended and restated bylaws, or our by-laws, to be in effect at the closing of this offering, which are filed as exhibits to the registration statement, of which this prospectus forms a part, and to the applicable provisions of the Delaware General Corporation Law. We refer in this section to our amended and restated certificate of incorporation as our certificate of incorporation, and we refer to our amended and restated by-laws as our by-laws.

Common stock

As of March 31, 2013, there were 319,946,737 shares of our common stock outstanding, including 2,506,114 shares of unvested restricted stock subject to repurchase by us, held of record by 50 stockholders, and assuming the conversion of all outstanding shares of preferred stock for shares of our common stock. Upon completion of this offering, there will be shares of our common stock outstanding.

Holders of our common stock are entitled to one vote for each share of common stock held of record for the election of directors and on all matters submitted to a vote of stockholders. Holders of our common stock are entitled to receive dividends ratably, if any, as may be declared by our board of directors out of legally available funds, subject to any preferential dividend rights of any preferred stock then outstanding. Upon our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in our net assets legally available after the payment of all our debts and other liabilities, subject to the preferential rights of any preferred stock then outstanding. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. Except as described below in Anti-takeover effects of Delaware law, our certificate of incorporation and our by-laws, a majority vote of common stockholders is generally required to take action under our certificate of incorporation and by-laws.

Preferred stock

Upon completion of this offering, our board of directors will be authorized, without action by the stockholders, to designate and issue up to an aggregate of shares of preferred stock in one or more series. The board of directors can fix the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of common stock. The issuance of preferred stock, while providing flexibility in connection with possible future financings and acquisitions and other corporate purposes could, under certain circumstances, have the effect of delaying or preventing a change in control of our company and might harm the market price of our common stock.

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Our board of directors will make any determination to issue such shares based on its judgment as to our best interests and the best interests of our stockholders. We have no current plans to issue any shares of preferred stock.

Certain of our stockholders hold, as of the date of this prospectus, 12,981,286 shares of our Series A-1 preferred stock, 22,304,324 shares of our Series A-2 preferred stock, 115,203,726 shares of our Series B preferred stock, 39,942,483 shares of our Series C preferred stock and 120,409,385 shares of our Series D preferred stock. Upon completion of this offering, each share of Series A-1, Series A-2, Series B, Series C and Series D preferred stock outstanding will be converted into our common stock on a -for-1 basis. Holders of substantially all of the shares of our preferred stock are subject to lock-up agreements with the underwriters that restrict the sale of our securities for 180 days following the date of this prospectus. See Underwriting for a description of these lock-up agreements

Warrants

As of March 31, 2013, warrants to purchase a total of 1,942,131 shares of our common stock were outstanding with a weighted average exercise price of $0.01 per share. These warrants expire beginning in March 2020.

As of March 31, 2013, warrants to purchase a total of 5,835,456 shares of our Series A-1 preferred stock were outstanding with an exercise price of $0.6619 per share. These warrants to purchase 5,835,456 Series A-1 preferred shares, which will be converted into warrants to purchase shares of common stock upon completion of this offering, are exercisable immediately and expire beginning in November 2015 through April 2019.

As of March 31, 2013, warrants to purchase a total of 574,800 shares of our Series B preferred stock were outstanding with an exercise price of $0.3262 per share. These warrants to purchase 574,800 Series B preferred shares, which will be converted into warrants to purchase shares of common stock upon completion of this offering, are exercisable immediately and expire in April 2019.

Registration rights

We entered into an amended and restated investors rights agreement, dated as of July 23, 2012, with the holders of shares of our common stock issuable upon conversion of the shares of preferred stock. These shares will represent approximately % of our outstanding common stock after this offering, or % if the underwriters exercise their option to purchase additional shares in full. These shares also may be sold under Rule 144 under the Securities Act of 1933, as amended, depending on their holding period and subject to restrictions in the case of shares held by persons deemed to be our affiliates.

Under the amended and restated investors rights agreement, holders of registrable shares can demand that we file a registration statement or request that their shares be included on a registration statement that we are otherwise filing, in either case, registering the resale of their shares of common stock. These registration rights are subject to conditions and limitations, including the right, in certain circumstances, of the underwriters of an offering to limit the number of shares included in such registration and our right, in certain circumstances, not to effect a requested S-1 registration within 60 days before or 180 days following any offering of our securities, including this offering or a requested S-3 registration within 30 days before or 90 days following any offering of our securities, including this offering.

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Demand registration rights

Following the six-month anniversary of the date of this prospectus, the holders of at least a majority of the registrable shares may require us to file a registration statement under the Securities Act on a Form S-1 or S-3, if available, at our expense with respect to the resale of their registrable shares, and we are required to use our best efforts to effect the registration.

Piggyback registration rights

If we propose to register any of our securities under the Securities Act for our own account or the account of any other holder, the holders of registrable shares are entitled to notice of such registration and to request that we include registrable shares for resale on such registration statement, subject to the right of any underwriter to limit the number of shares included in such registration.

We will pay all registration expenses, other than underwriting discounts and commissions, related to any demand or piggyback registration. The amended and restated investors rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders, in the event of misstatements or omissions in the registration statement attributable to us except in the event of fraud and they are obligated to indemnify us for misstatements or omissions attributable to them.

The registration rights will terminate upon the later of the date on which all registrable shares have been sold and the fifth anniversary of the closing date of this offering.

Voting agreement and right of first refusal and co-sale agreement

We entered into an amended and restated voting agreement and an amended and restated right of first refusal and co-sale agreement, each dated as of July 23, 2012, with all holders of our preferred stock and certain holders of our common stock. These agreements provide for certain rights and obligations, such as board composition requirements and stock transfer restrictions. These agreements will terminate upon the completion of this offering; however, the lock-up provision under the amended and restated right of first refusal and co-sale agreement will survive termination pursuant to the terms of the agreement. The lock-up provision under the investors rights agreement shall also survive the completion of this offering. See Shares eligible for future sales Lock-up agreements.

Anti-takeover effects of Delaware law, our certificate of incorporation and our by-laws

Our certificate of incorporation and by-laws include a number of provisions that may have the effect of encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board composition and filling vacancies

In accordance with our certificate of incorporation, our board is divided into three classes serving three-year terms, with one class being elected each year. Our certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote

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of the holders of 75% or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office, even if less than a quorum.

No written consent of stockholders

Our certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting.

Meetings of stockholders

Our by-laws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our by-laws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance notice requirements

Our by-laws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days or more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. The notice must contain certain information specified in the by-laws. These provisions may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer s own slate of directors or otherwise attempting to obtain control of our company.

Amendment to by-laws and certificate of Incorporation

As required by the Delaware General Corporation Law, any amendment of our certificate of incorporation must first be approved by a majority of our board of directors and, if required by law or our certificate of incorporation, thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment, and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, directors, limitation of liability, exclusive jurisdiction of Delaware Courts and the amendment of our by-laws and certificate of incorporation must be approved by not less than 75% of the outstanding shares entitled to vote on the amendment, and not less than 75% of the outstanding shares of each class entitled to vote thereon as a class. Our by-laws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the by-laws; and may also be amended by the affirmative vote of at least 75% of the outstanding shares entitled to vote on the amendment, or, if the board of directors recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class.

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Blank check preferred stock

Our certificate of incorporation provides for authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of us or our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Section 203 of the Delaware General Corporation Law

Upon completion of this offering, we will be subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. A business combination includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, 15% or more of the corporation s voting stock.

Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or
- at or after the time the stockholder became interested, the business combination was approved by the board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

A Delaware corporation may opt out of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or by-laws resulting from a stockholders amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

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Exclusive jurisdiction of certain actions

Our certificate of incorporation requires, to the fullest extent permitted by law, that derivative actions brought in our name, actions against our directors, officers and employees for breach of fiduciary duty and other similar actions may be brought only in the Court of Chancery in the State of Delaware, unless we otherwise consent. Although we believe this provision benefits us by providing increased consistency in the application of Delaware law in the types of lawsuits to which it applies, the provision may have the effect of discouraging lawsuits against our directors and officers.

Nasdaq Global Market listing

We have applied for listing of our common stock on The Nasdaq Global Market under the trading symbol BLUE.

Transfer agent and registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

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Shares eligible for future sale

Prior to this offering, there has been no public market for our common stock. Future sales of our common stock, including shares issued upon the exercise of outstanding options or warrants, in the public market after this offering, or the perception that those sales may occur, could cause the prevailing market price for our common stock to fall or impair our ability to raise equity capital in the future. As described below, only a limited number of shares of our common stock will be available for sale in the public market for a period of several months after completion of this offering due to contractual and legal restrictions on resale described below. Future sales of our common stock in the public market either before (to the extent permitted) or after restrictions lapse, or the perception that those sales may occur, could adversely affect the prevailing market price of our common stock at such time and our ability to raise equity capital at a time and price we deem appropriate.

Sale of restricted shares

As of March 31, 2013, based on the number of shares of our common stock then outstanding, upon the closing of this offering and assuming (1) the conversion of our outstanding preferred stock into common stock, (2) no exercise of the underwriters option to purchase additional shares of common stock and (3) no exercise of outstanding options or warrants, we would have had outstanding an aggregate of approximately shares of common stock. Of these shares, all of the shares of common stock to be sold in this offering, and any shares sold upon exercise of the underwriters option to purchase additional shares will be freely tradable in the public market without restriction or further registration under the Securities Act of 1933, as amended, or the Securities Act, unless the shares are held by any of our affiliates as such term is defined in Rule 144 of the Securities Act. All remaining shares of common stock held by existing stockholders immediately prior to the completion of this offering will be restricted securities as such term is defined in Rule 144. These restricted securities were issued and sold by us, or will be issued and sold by us, in private transactions and are eligible for public sale only if registered under the Securities Act or if they qualify for an exemption from registration under the Securities Act, including the exemptions provided by Rule 144 or Rule 701, which rules are summarized below.

As a result of the lock-up agreements referred to below and the provisions of Rule 144 and Rule 701 under the Securities Act, the shares of our common stock (excluding the shares sold in this offering) that will be available for sale in the public market are as follows:

Approximate Number of Shares	First Date Available for Sale into Public Market
	180 days after the date of this prospectus upon expiration of the lock-up agreements referred to below, subject in some cases to applicable volume limitations under Rule 144

Lock-up agreements

In connection with this offering, we, our directors, our executive officers and stockholders holding approximately % of our shares of common stock outstanding as of March 31, 2013 (assuming conversion of all of our outstanding shares of preferred stock), and substantially all of our option holders who are not also stockholders have agreed, subject to certain exceptions, with the underwriters not to dispose of or hedge any shares of our common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of

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the lock-up agreement continuing through the date 180 days after the date of this prospectus, except with the prior written consent of J.P. Morgan Securities LLC and Merrill Lynch, Pierce, Fenner & Smith Incorporated, together the representatives of the underwriters. The representatives of the underwriters have advised us that they have no current intent or arrangement to release any of the shares subject to the lock-up agreements prior to the expiration of the lock-up period.

Following the lock-up periods set forth in the agreements described above, and assuming that the representatives of the underwriters do not release any parties from these agreements, all of the shares of our common stock that are restricted securities or are held by our affiliates as of the date of this prospectus will be eligible for sale in the public market in compliance with Rule 144 under the Securities Act.

In addition, pursuant to each of our amended and restated investors rights agreement and amended and restated right of first refusal and co-sale agreement, the parties thereto have agreed that, if requested in writing by the representatives of the underwriters of the initial public offering of our securities, they will not sell, make any short sale of, grant any option for the purchase of, or otherwise dispose of any shares of our stock during the same 180-day restricted period referred to above. We expect the representatives of the underwriters to invoke this written request prior to the completion of this offering and, accordingly, that the parties to these agreements will be subject to the related transaction restrictions.

Holders of approximately shares of common stock (including shares of our preferred stock that will be converted into shares of our common stock upon completion of this offering), or % of our outstanding shares of common stock on an as converted basis, are, collectively subject to lock-up restrictions as parties to these agreements or lock-up agreements with the underwriters.

Rule 144

In general, under Rule 144, as currently in effect, once we have been subject to the public company reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, for at least 90 days, a person (or persons whose shares are required to be aggregated) who is not deemed to have been one of our affiliates for purposes of Rule 144 at any time during the three months preceding a sale, and who has beneficially owned restricted securities within the meaning of Rule 144 for at least six months, including the holding period of any prior owner other than one of our affiliates, is entitled to sell those shares in the public market (subject to the lock-up agreement referred to above, if applicable) without complying with the manner of sale, volume limitations or notice provisions of Rule 144, but subject to compliance with the public information requirements of Rule 144. If such a person has beneficially owned the sales proposed to be sold for at least one year, including the holding period of any prior owner other than affiliates, then such person is entitled to sell such shares in the public market without complying with any of the requirements of Rule 144 (subject to the lock-up agreement referred to above, if applicable). In general, under Rule 144, as currently in effect, once we have been subject to the public company reporting requirements of the Exchange Act for at least 90 days, our affiliates, as defined in Rule 144, who have beneficially owned the shares proposed to be sold for at least six months are entitled to sell in the public market, upon expiration of any applicable lock-up agreements and within any three-month period, a number of those shares of our common stock that does not exceed the greater of:

- one percent of the number of common shares then outstanding, which will equal approximately shares of common stock immediately after this offering (calculated

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on the basis of the number of shares of our common stock outstanding as of , the assumptions described above and assuming no exercise of the underwriter s option to purchase additional shares and no exercise of outstanding options or warrants); or

the average weekly trading volume of our common stock on The Nasdaq Global Market during the four calendar weeks preceding the filing of a notice on Form 144 with respect to such sale.

Such sales under Rule 144 by our affiliates or persons selling shares on behalf of our affiliates are also subject to certain manner of sale provisions, notice requirements and to the availability of current public information about us. Notwithstanding the availability of Rule 144, the holders of substantially all of our restricted securities have entered into lock-up agreements as referenced above and their restricted securities will become eligible for sale (subject to the above limitations under Rule 144) upon the expiration of the restrictions set forth in those agreements.

Rule 701

In general, under Rule 701 as currently in effect, any of our employees, directors, officers, consultants or advisors who acquired common stock from us in connection with a written compensatory stock or option plan or other written agreement in compliance with Rule 701 under the Securities Act before the effective date of the registration statement of which this prospectus is a part (to the extent such common stock is not subject to a lock-up agreement) is entitled to rely on Rule 701 to resell such shares beginning 90 days after we become subject to the public company reporting requirements of the Exchange Act in reliance on Rule 144, but without compliance with the holding period requirements contained in Rule 144. Accordingly, subject to any applicable lock-up agreements, beginning 90 days after we become subject to the public company reporting requirements of the Exchange Act, under Rule 701 persons who are not our affiliates, as defined in Rule 144, may resell those shares without complying with the minimum holding period or public information requirements of Rule 144, and persons who are our affiliates may resell those shares without compliance with Rule 144 s minimum holding period requirements (subject to the terms of the lock-up agreement referred to below, if applicable).

Equity incentive plans

We intend to file with the Securities and Exchange Commission a registration statement under the Securities Act covering the shares of common stock that we may issue upon exercise of outstanding options reserved for issuance under the 2002 Employee, Director and Consultant Plan, the 2010 Stock Option and Grant Plan and the 2013 Stock Option and Incentive Plan. Such registration statement is expected to be filed and become effective as soon as practicable after the completion of this offering. Accordingly, shares registered under such registration statement will be available for sale in the open market following its effective date, subject to Rule 144 volume limitations and the lock-up agreements described above, if applicable.

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Material U.S. federal income tax considerations for non-U.S. holders

The following is a summary of the material U.S. federal income tax considerations of the ownership and disposition of our common stock to non-U.S. holders. It is not intended to be a complete analysis of all the U.S. federal income tax considerations that may be relevant to non-U.S. holders. This summary is based upon the provisions of the Internal Revenue Code of 1986, as amended, or the Code, Treasury regulations promulgated thereunder, administrative rulings and judicial decisions, all as of the date hereof. These authorities may be changed, possibly with retroactive effect, which may result in U.S. federal income tax consequences different from those set forth below. We have not sought any ruling from the Internal Revenue Service, or the IRS, with respect to the statements made and the conclusions reached in the following summary. There can be no assurance that the IRS will agree with such statements and conclusions or that any contrary position taken by the IRS would not be sustained by a court.

This summary also does not address the tax considerations arising under the laws of any foreign, state or local jurisdiction. In addition, this discussion does not address tax considerations applicable to an investor s particular circumstances or to investors that may be subject to special tax rules, including, without limitation:

banks, insurance companies or other financial institutions;

persons subject to the alternative minimum tax;

tax-exempt organizations;

an integral part or controlled entity of a foreign sovereign;

dealers in securities or currencies;

traders in securities that elect to use a mark-to-market method of accounting for their securities holdings;

persons that own, or are deemed to own, more than five percent of our capital stock (except to the extent specifically set forth below);

controlled foreign corporations or passive foreign investment companies

certain former citizens or long-term residents of the United States;

persons who hold our common stock as a position in a hedging transaction, straddle, conversion transaction or other risk reduction transaction;

persons deemed to sell our common stock under the constructive sale provisions of the Code; or

persons who hold our common stock other than as a capital asset (generally, an asset held for investment purposes).

If an entity that is classified as a partnership for U.S. federal income tax purposes holds our common stock, the tax treatment of persons treated as its partners for U.S. federal income tax purposes will generally depend upon the status of the partner and the activities of the partnership. Prospective investors that are classified as partnerships for U.S. federal income tax purposes and prospective investors that may hold our common stock through an entity classified as a partnership for U.S. federal income tax purposes, should consult their own tax advisors.

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YOU ARE URGED TO CONSULT YOUR TAX ADVISOR WITH RESPECT TO THE APPLICATION OF THE UNITED STATES FEDERAL INCOME TAX LAWS TO YOUR PARTICULAR SITUATION, AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE UNITED STATES FEDERAL ESTATE OR GIFT TAX RULES OR UNDER THE LAWS OF ANY STATE, LOCAL, FOREIGN OR OTHER TAXING JURISDICTION OR UNDER ANY APPLICABLE TAX TREATY.

Non-U.S. holder defined

For purposes of this discussion, you are a non-U.S. holder if you are a holder that, for U.S. federal income tax purposes, is not a U.S. person or a partnership. For purposes of this discussion, you are a U.S. person if you are:

- an individual citizen or resident of the United States;
- a corporation or other entity taxable as a corporation created or organized in the United States or under the laws the United States or any political subdivision thereof;
- an estate whose income is subject to U.S. federal income tax regardless of its source; or
- a trust (a) if a court within the United States is able to exercise primary jurisdiction over the administration of the trust and one or more U.S. persons have the authority to control all substantial decisions of the trust or (b) that has made an election to be treated as a U.S. person.

Distributions

We have not made any distributions on our common stock and do not plan to make any distributions for the foreseeable future. However, if we do make distributions on our common stock, those payments will constitute dividends for U.S. tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent those distributions exceed both our current and our accumulated earnings and profits, they will constitute a return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock, which will be subject to tax as described in Gain on Disposition of Common Stock, below.

Any dividend paid to you generally will be subject to U.S. withholding tax either at a rate of 30% of the gross amount of the dividend or such lower rate as may be specified by an applicable income tax treaty. In order to receive a reduced treaty rate, you must provide us with an IRS Form W-8BEN or other appropriate version of IRS Form W-8 certifying qualification for the reduced rate.

Dividends received by you that are effectively connected with your conduct of a U.S. trade or business are exempt from such withholding tax. In order to obtain this exemption, you must provide us with an IRS Form W-8ECI properly certifying such exemption. Such effectively connected dividends, although not subject to withholding tax, are taxed at the same graduated rates applicable to U.S. persons, net of certain deductions and credits. In addition, if you are a corporate non-U.S. holder, dividends you receive that are effectively connected with your conduct of a U.S. trade or business may also be subject to a branch profits tax at a rate of 30% or such lower rate as may be specified by an applicable income tax treaty.

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If you are eligible for a reduced rate of withholding tax pursuant to a tax treaty, you may obtain a refund of any excess amounts withheld if you file an appropriate claim for refund with the IRS in a timely manner.

Gain on disposition of common stock

You generally will not be required to pay U.S. federal income tax on any gain realized upon the sale or other disposition of our common stock unless:

- the gain is effectively connected with your conduct of a U.S. trade or business;
- you are an individual non-U.S. holder who holds our common stock as a capital asset, who is present in the United States for a period or periods aggregating 183 days or more during the calendar year in which the sale or disposition occurs and certain other conditions are met; or
- our common stock constitutes a U.S. real property interest by reason of our status as a United States real property holding corporation for U.S. federal income tax purposes, or a USRPHC, at any time within the shorter of the five-year period preceding the disposition or your holding period for our common stock.

If you are a non-U.S. holder described in the first bullet above, you will be required to pay tax on the net gain derived from the sale under regular graduated U.S. federal income tax rates. Corporate non-U.S. holders described in the first bullet above may be subject to the branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual non-U.S. holder described in the second bullet above, you will be required to pay a flat 30% tax on the gain derived from the sale, which may be offset by U.S.-source capital losses (even though you are not considered a resident of the United States). You should consult any applicable income tax or other treaties, which may provide different rules.

We believe that we are not currently and do not anticipate becoming a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property relative to the fair market value of our other business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we become a USRPHC, however, as long as our common stock is treated for federal income tax purposes as regularly traded on an established securities market during the applicable calendar year, such common stock will not be treated as U.S. real property interests unless you actually or constructively hold more than five percent of such regularly traded common stock at any time during the shorter of the five-year period preceding the disposition or your holding period for our common stock. However, no assurance can be provided that our common stock will be treated as regularly traded on an established securities market for purposes of the rules described above. If we were treated as a USRPHC during the applicable period and the exception described above did not apply, gain on the sale or other taxable disposition of our stock will be subject to tax in the same manner as gain that is effectively connected with the conduct of a U.S. trade or business, except that the branch profits tax will not apply.

Backup withholding and information reporting

Generally, we must report annually to the IRS the amount of dividends paid to you, your name and address, and the amount of tax withheld, if any. A similar report will be sent to you. Pursuant to applicable income tax treaties or other agreements, the IRS may make these reports available to tax authorities in your country of residence.

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Payments of dividends or of proceeds on the disposition of stock made to you may be subject to information reporting and backup withholding (currently at a rate of 28%) unless you establish an exemption, for example by properly certifying your non-U.S. status on a Form W-8BEN or another appropriate version of IRS Form W-8. Notwithstanding the foregoing, backup withholding and information reporting may apply if either we or our paying agent has actual knowledge, or reason to know, that you are a U.S. person.

Backup withholding is not an additional tax; rather, the U.S. income tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund or credit may be obtained, provided that the required information is furnished to the IRS in a timely manner.

FATCA withholding and information reporting

Legislation enacted in March 2010, commonly referred to as FATCA, will impose United States federal withholding at a rate of 30% on payments to certain non-U.S. entities (including financial intermediaries), including dividends on and the gross proceeds from dispositions of our common stock, unless various information reporting and due diligence requirements, which are different from and in addition to the certification requirements described elsewhere in this discussion, have been satisfied (generally relating to ownership by U.S. persons of interests in or accounts with those entities). The withholding rules applicable to payments of dividends on our common stock will be phased in beginning January 1, 2014. The withholding rules will apply to gross proceeds from dispositions of U.S. common stock beginning January 1, 2017. Although Treasury regulations implementing FATCA were recently finalized, these rules remain unclear in several respects and are subject to material changes. Prospective investors should consult their tax advisors regarding the possible implications of FATCA on their investment in our common stock.

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Underwriting

We are offering the shares of common stock described in this prospectus through a number of underwriters. J.P. Morgan Securities LLC and Merrill Lynch, Pierce, Fenner & Smith Incorporated are acting as joint book-running managers of the offering and as representatives of the underwriters. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover of this prospectus, the number of shares of common stock listed next to its name in the following table:

Name	Number of shares
J.P. Morgan Securities LLC	
Merrill Lynch, Pierce, Fenner & Smith Incorporated	
Cowen and Company, LLC	
Canaccord Genuity Inc.	
Wedbush Securities Inc.	
Total	

The underwriters are committed to purchase all the shares of common stock offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

The underwriters propose to offer the shares of common stock directly to the public at the initial public offering price set forth on the cover of this prospectus and to certain dealers at that price less a concession not in excess of $ per share. Any such dealers may resell shares to certain other brokers or dealers at a discount of up to $ per share from the initial public offering price. After the initial public offering of the shares, the offering price and other selling terms may be changed by the underwriters. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

The underwriters have an option to buy up to additional shares of common stock from us to cover sales of shares by the underwriters which exceed the number of shares specified in the table above. The underwriters have 30 days from the date of this prospectus to exercise this option to purchase additional shares. If any shares are purchased with this option to purchase additional shares, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

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The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting fee is $ per share. The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters assuming both no exercise and full exercise of the underwriters option to purchase additional shares.

	Without exercise of option to purchase additional shares	With full exercise of option to purchase additional shares
Per share	$	$
Total	$	$

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately $.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We have agreed that we will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, or file with the Securities and Exchange Commission a registration statement under the Securities Act of 1933, as amended (the Securities Act), relating to, any shares of our common stock or any securities convertible into or exchangeable or exercisable for any shares of our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (ii) enter into any swap or other arrangement that transfers all or a portion of the economic consequences associated with the ownership of any shares of our common stock or any such other securities (regardless of whether any of these transactions are to be settled by the delivery of shares of our common stock or such other securities, in cash or otherwise), in each case without the prior written consent of J.P. Morgan Securities LLC and Merrill Lynch, Pierce, Fenner & Smith Incorporated for a period of 180 days after the date of this prospectus, other than the shares of our common stock to be sold hereunder and any shares of our common stock issued upon the exercise of options granted under our existing management incentive plans.

Our directors and executive officers, and certain of our significant shareholders have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant to which each of these persons or entities, with limited exceptions, for a period of 180 days after the date of this prospectus, may not, without the prior written consent of J.P. Morgan Securities LLC and Merrill Lynch, Pierce, Fenner & Smith Incorporated, (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock (including without limitation, common stock or such other

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securities which may be deemed to be beneficially owned by such directors, executive officers and shareholders in accordance with the rules and regulations of the Securities and Exchange Commission and securities which may be issued upon exercise of a stock option or warrant), or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933, as amended.

We have applied to have our common stock approved for listing/quotation on The Nasdaq Global Market under the symbol BLUE.

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be covered shorts, which are short positions in an amount not greater than the underwriters option to purchase additional shares referred to above, or may be naked shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional shares, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the option to purchase additional shares. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on The Nasdaq Global Market, in the over-the-counter market or otherwise.

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Prior to this offering, there has been no public market for our common stock. The initial public offering price will be determined by negotiations between us and the representatives of the underwriters. In determining the initial public offering price, we and the representatives of the underwriters expect to consider a number of factors including:

- the information set forth in this prospectus and otherwise available to the representatives;
- our prospects and the history and prospects for the industry in which we compete;
- an assessment of our management;
- our prospects for future earnings;
- the general condition of the securities markets at the time of this offering;
- the recent market prices of, and demand for, publicly traded common stock of generally comparable companies; and
- other factors deemed relevant by the underwriters and us.

Neither we nor the underwriters can assure investors that an active trading market will develop for our common shares, or that the shares will trade in the public market at or above the initial public offering price.

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

This document is only being distributed to and is only directed at (i) persons who are outside the United Kingdom or (ii) to investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, or the Order, or (iii) high net worth entities, and other persons to whom it may lawfully be communicated, falling with Article 49(2)(a) to (d) of the Order (all such persons together being referred to as relevant persons). The securities are only available to, and any invitation, offer or agreement to subscribe, purchase or otherwise acquire such securities will be engaged in only with, relevant persons. Any person who is not a relevant person should not act or rely on this document or any of its contents.

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive, each, a Relevant Member State, from and including the date on which the European Union Prospectus Directive, or the EU Prospectus Directive, was implemented in that Relevant Member State, or the Relevant Implementation Date, an offer of securities described in this prospectus may not be made to the public in that Relevant Member State prior to the publication of a prospectus in relation to the shares which has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another

Relevant Member State and notified to the competent authority in that Relevant Member State,

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all in accordance with the EU Prospectus Directive, except that, with effect from and including the Relevant Implementation Date, an offer of securities described in this prospectus may be made to the public in that Relevant Member State at any time:

- to any legal entity which is a qualified investor as defined under the EU Prospectus Directive;
- to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the EU Prospectus Directive); or
- in any other circumstances falling within Article 3(2) of the EU Prospectus Directive, provided that no such offer of securities described in this prospectus shall result in a requirement for the publication by us of a prospectus pursuant to Article 3 of the EU Prospectus Directive.

For the purposes of this provision, the expression an offer of securities to the public in relation to any securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the same may be varied in that Member State by any measure implementing the EU Prospectus Directive in that Member State. The expression EU Prospectus Directive means Directive 2003/71/EC (and any amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State) and includes any relevant implementing measure in each Relevant Member State, and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Notice to prospective investors in Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or the SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this prospectus nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this prospectus nor any other offering or marketing material relating to the offering, the Company, the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, and the offer of shares

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has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or the CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to prospective investors in the Dubai International Financial Centre

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or the DFSA. This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The shares to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus you should consult an authorized financial advisor.

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Legal matters

The validity of the issuance of our common stock offered in this prospectus will be passed upon for us by Goodwin Procter LLP, Boston, Massachusetts. Certain legal matters in connection with this offering will be passed upon for the underwriters by Ropes & Gray LLP, Boston, Massachusetts.

Experts

The consolidated financial statements as of December 31, 2011, and for the year then ended, appearing in this Prospectus and Registration Statement have been audited by McGladrey LLP, an independent registered public accounting firm, as stated in their report appearing elsewhere herein, and are included in reliance upon such report and upon the authority of such firm as experts in accounting and auditing.

The consolidated financial statements of bluebird bio, Inc. at December 31, 2012, and for the year then ended, appearing in this Prospectus and Registration Statement have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon appearing elsewhere herein, and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

Where you can find more information

We have filed with the Securities and Exchange Commission, or SEC, a registration statement on Form S-1, or the registration statement, under the Securities Act of 1933, as amended, with respect to the shares of common stock offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement or the exhibits and schedules filed therewith. For further information with respect to bluebird bio, Inc. and the common stock offered hereby, reference is made to the registration statement and the exhibits and schedules filed therewith. Statements contained in this prospectus regarding the contents of any contract or any other document that is filed as an exhibit to the registration statement are not necessarily complete, and each such statement is qualified in all respects by reference to the full text of such contract or other document filed as an exhibit to the registration statement. A copy of the registration statement and the exhibits and schedules filed therewith may be inspected without charge at the public reference room maintained by the SEC, located at 100 F Street N.E., Washington, D.C. 20549, and copies of all or any part of the registration statement may be obtained from such offices upon the payment of the fees prescribed by the SEC. Please call the SEC at 1-800-SEC-0330 for further information about the public reference room. The SEC also maintains a website that contains reports, proxy and information statements and other information regarding registrants that file electronically with the SEC. The address is www.sec.gov.

Upon completion of this offering, we will become subject to the information and periodic reporting requirements of the Securities Exchange Act of 1934, as amended, and, in accordance therewith, will file periodic reports, proxy statements and other information with the SEC. Such periodic reports, proxy statements and other information will be available for inspection and copying at the public reference room and website of the SEC referred to above. We maintain a website at www.bluebirdbio.com. The reference to our website address does not constitute incorporation by reference of the information contained on our website, and you should not consider the contents of our website in making an investment decision with respect to our common stock.

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Glossary

AAV	adeno-associated virus
ACALD	adult cerebral adrenoleukodystrophy, a type of ALD that develops in males 15 years or older
ALD	adrenoleukodystrophy, a rare X-linked, inherited, neurological disorder caused by mutations in the ABCD1 gene
ALDP	ALD protein, a protein that plays a critical role in the breakdown and metabolism of VLCFA
AMN	adrenomyeloneuropathy, the most common form of ALD, typically developing in adults 21 years or older
ANSM	l agence nationale de sécurité du médicament et des produits de santé (France)
BLA	Biologics License Application
CAR	chimeric antigen receptor
CBER	FDA Center for Biologics Evaluation and Research
CCALD	childhood cerebral adrenoleukodystrophy, the most severe form of ALD, typically developing in boys between ages of 3 and 15
CIRM	California Institute for Regenerative Medicine
CMC	chemical, manufacturing and control
CMS	Centers for Medicare & Medicaid Services, an agency within the U.S. Department of Health and Human Services
CRO	contract research organization
CTA	clinical trial application
CTGTAC	Cellular, Tissue and Gene Therapies Advisory Committee
DNA	deoxyribonucleic acid,
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GCP	good clinical practices
GLP	good laboratory practices
GMP	good manufacturing practices
GTP	good tissue practices
GVHD	graft-versus-host disease
HCT/P	human cells, tissues, and cellular and tissue based product
HIV-1	Human Immunodeficiency Virus Type 1
HLA	Human-Leukocyte-Antigen
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplant, an approach of treating a patient with HSCs contributed by a donor that contain a functioning copy of the gene underlying the disease.
IBC	institutional biosafety commitee
IND	Investigational New Drug application
Inserm	institut national de la santé et de la recherché médicale (France), or the French Institute of Health and Medical Research
IRB	institutional review board
IVIM	in vitro immortalization
MAA	Marketing Authorization Application
MFDs	major functional disabilities
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)

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MRI	magnetic resonance imaging
NDA	new drug application
NFS	Neurological Function Score
NIH	U.S. National Institutes of Health
OBA	NIH Office of Biotechnology Activities
OCTGT	FDA Office of Cellular, Tissue and Gene Therapies
PDCO	EMA Pediatric Committee
PIP	Pediatric Investigation Plan
RAC	NIH Office of Biotechnology Activities Recombinant DNA Advisory Committee
RBC	red blood cell
REMS	Risk Evaluation and Mitigation Strategy
SCD	sickle cell disease
TTCF	ten tray cell factories
VLCFA	very long-chain fatty acids

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bluebird bio, Inc.

Index to consolidated financial statements

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Report of independent registered public accounting firm

The Board of Directors and Stockholders

bluebird bio, Inc.

We have audited the accompanying consolidated balance sheet of bluebird bio, Inc. as of December 31, 2012 and the related consolidated statement of operations and comprehensive loss, convertible preferred stock and stockholders (deficit) equity, and cash flows for the year then ended. 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 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 the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company s internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company s internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audit provides 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, 2012, and the consolidated results of its operations and its cash flows for the year then ended, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts

March 21, 2013

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Report of independent registered public accounting firm

The Board of Directors and Stockholders of

bluebird bio, Inc.

Cambridge, Massachusetts

We have audited the accompanying consolidated balance sheet of bluebird bio, Inc. as of December 31, 2011, and the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders deficit, and cash flows for the year then ended. 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 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 the financial statements are free of material misstatement. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company s internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of bluebird bio, Inc. as of December 31, 2011, and the results of its operations and its cash flows for the year then ended, in conformity with U.S. generally accepted accounting principles.

/s/ McGladrey LLP

Boston, Massachusetts

March 21, 2013

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bluebird bio, Inc.

Consolidated balance sheets

(In thousands, except per share data)

	December 31,			Pro forma March 31,
	2011	2012	2013	2013
		Actual	(unaudited)	
Assets				
Current assets:				
Cash and cash equivalents	$ 25,604	$ 67,011	$ 131,836	$ 131,836
Marketable securities	3,507			
Prepaid expenses and other current assets	869	773	3,253	3,253
Total current assets	29,980	67,784	135,089	135,089
Property and equipment, net	728	1,288	2,120	2,120
Restricted cash	210	250	250	250
Total assets	$ 30,918	$ 69,322	$ 137,459	$ 137,459
Liabilities, convertible preferred stock, and stockholders (deficit) equity				
Current liabilities:				
Accounts payable	$ 1,793	$ 2,173	$ 2,227	$ 2,227
Accrued expenses and other current liabilities	760	2,115	2,132	2,132
Deferred revenue, current portion	340	340	25,340	25,340
Total current liabilities	2,893	4,628	29,699	29,699
Warrant liability	637	215	256	
Deferred rent, net of current portion	13	46	46	46
Deferred revenue, net of current portion	679	340	49,213	49,213
Total liabilities	4,222	5,229	79,214	78,958
Commitments and contingencies *(Note 8)*				
Series A-1 convertible preferred stock, $0.01 par value, 18,817 shares authorized; 12,981 shares issued and outstanding at December 31, 2011, and no shares issued and outstanding pro forma (unaudited)	9,217			
Series A-2 convertible preferred stock, $0.01 par value, 22,304 shares authorized; 22,304 shares issued and outstanding at December 31, 2011 and 2012 and March 31, 2013 (unaudited), and no shares issued and outstanding pro forma (unaudited) (aggregate liquidation preference of $12,843)	15,837	7,137	7,137	
Series B convertible preferred stock, $0.01 par value, 115,779 shares authorized; 115,204 shares issued and outstanding at December 31, 2011 and 2012 and March 31, 2013 (unaudited), and no shares issued and outstanding pro forma (unaudited) (aggregate liquidation preference of $56,369)	41,495	40,321	40,321	
Series C convertible preferred stock, $0.01 par value, 39,943 shares authorized; 39,943 shares issued and outstanding at December 31, 2011 and 2012 and March 31, 2013 (unaudited), and no shares issued and outstanding pro forma (unaudited) (aggregate liquidation preference of $15,000)	15,854	12,382	12,382	
Series D convertible preferred stock, $0.01 par value, 120,409 shares authorized; no shares, 120,409 and 120,409 shares issued and outstanding at December 31, 2011 and 2012 and March 31, 2013 (unaudited), respectively, and no shares issued and outstanding pro forma (unaudited) (aggregate liquidation preference of $60,000)		60,000	60,000	
Stockholders (deficit) equity:				
Series A-1 convertible preferred stock, $0.01 par value, 18,817 shares authorized; 12,981 shares issued and outstanding at December 31, 2012 and March 31, 2013 (unaudited), and no shares issued and outstanding pro forma (unaudited) (no liquidation preference)		2,337	2,337	
	39	59	66	3,174

Common stock,$0.01 par value, 408,000 shares authorized; 3,895, 5,864, and 6,599 shares issued and outstanding at December 31, 2011 and 2012 and March 31, 2013 (unaudited), respectively, and 317,440 shares issued and outstanding pro forma (unaudited)				
Additional paid-in capital	7,695	15,211	15,900	135,225
Accumulated other comprehensive income	1			
Accumulated deficit	(63,442)	(73,354)	(79,898)	(79,898)
Total stockholders (deficit) equity	(55,707)	(55,747)	(61,595)	58,501
Total liabilities, convertible preferred stock and stockholders (deficit) equity	$ 30,918	$ 69,322	$ 137,459	$ 137,459

See accompanying notes to consolidated financial statements.

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bluebird bio, Inc.

Consolidated statements of operations and comprehensive loss

(In thousands, except per share data)

	Year ended December 31,		Three months ended March 31,	
	2011	2012	2012	2013
			(unaudited)	
Revenue:				
Collaboration revenue	$	$	$	$ 1,042
Research and license fees	640	340	85	85
Grant revenue	242			
Total revenue	882	340	85	1,127
Expenses:				
Research and development	11,409	17,210	3,858	5,284
General and administrative	4,615	6,846	1,363	2,324
Total expenses	16,024	24,056	5,221	7,608
Loss from operations	(15,142)	(23,716)	(5,136)	(6,481)
Other (expense) income, net:				
Interest income	5	5	1	3
Foreign currency (losses) gains	(100)	13	8	(25)
Re-measurement of warrants	(361)	28	59	(41)
Other (expense) income, net	(456)	46	68	(63)
Net loss	$ (15,598)	$ (23,670)	$ (5,068)	$ (6,544)
Other comprehensive income (loss):				
Foreign currency translation adjustment	72			
Unrealized gains (losses) on marketable securities	1	(1)		
Total other comprehensive income (loss)	73	(1)		
Comprehensive loss	$ (15,525)	$ (23,671)	$ (5,068)	$ (6,544)
Reconciliation of net loss to net loss applicable to common stockholders:				
Net loss	$ (15,598)	$ (23,670)	$ (5,068)	$ (6,544)
Accretion and dividends on convertible preferred stock	(4,993)	(3,057)	(1,285)	
Gain on extinguishment of convertible preferred stock		23,114		
Net loss applicable to common stockholders	$ (20,591)	$ (3,613)	$ (6,353)	$ (6,544)

Net loss per share applicable to common stockholders basic and diluted	$ (9.01)	$ (0.73)	$ (1.50)	$ (1.05)
Weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted	2,285	4,972	4,236	6,226
Pro forma net loss per share applicable to common stockholders basic and diluted (unaudited)		$ (0.10)		$ (0.02)
Pro forma weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted (unaudited)		248,700		317,067

See accompanying notes to consolidated financial statements.

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bluebird bio, Inc.

Consolidated statements of convertible preferred stock and stockholders (deficit) equity

(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		Series A-1 convertible preferred stock		Common stock		Additional paid-in capital	Accum-ulated other compre-hensive income (loss)	Accum-ulated deficit	Total stock-holders (deficit) equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2010	**12,981**	**$ 8,760**	**22,304**	**$ 15,246**	**61,556**	**$ 21,000**		**$**		**$**		**$**	**1,576**	**$ 16**	**$ 11,817**	**$ (72)**	**$ (47,844)**	**$ (36,083)**
Issuance of Series C Preferred Stock, net of issuance costs							39,943	14,904										
Issuance of Series B Preferred Stock					53,648	17,500												
Accretion and dividends on convertible preferred stock		457		591		2,995		950							(4,993)			**(4,993)**
Issuance of restricted stock													273	3	27			**30**
Issuance of restricted stock in exchange for consulting services																		