bluebird bio, Inc.
Form 424B4
June 19, 2013
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Filed Pursuant to Rule 424(b)(4)
Registration No. 333-188605
Registration No. 333-189430

Prospectus

5,941,176 shares

Common stock

This is an initial public offering of common stock by bluebird bio, Inc. We are selling 5,941,176 shares of common stock.

Prior to this offering, there has been no public market for our common stock. Our common stock has been approved for listing on The Nasdaq Global Select 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	$ 17.00	$ 100,999,992
Underwriting discounts and commissions(1)	$ 1.19	$ 7,069,999
Proceeds to bluebird bio, before expenses	$ 15.81	$ 93,929,993

(1) The underwriters will receive compensation in addition to the underwriting discount. See Underwriting beginning on page 191.
We have granted the underwriters an option for a period of 30 days to purchase up to 891,176 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 June 24, 2013.

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

Cowen and Company

Canaccord Genuity **Wedbush PacGrow Life Sciences**

June 18, 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 a Phase I/II clinical study in the United States and have initiated a Phase I/II clinical study in 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

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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.

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 worldwide incidence rate for adrenoleukodystrophy, or ALD, the superset of CCALD, is approximately one in 20,000 newborn males; CCALD accounts for about 30-40% of patients diagnosed with ALD.

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. It has been estimated that about 1.5% (80 to 90 million people) of the global population are carriers of ß-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. According to Thalassemia International Federation, about 288,000 patients with ß-thalassemia major are alive and registered as receiving regular treatment around the world, of which it is estimated that about 15,000 live in the United States and Europe. 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 have initiated this study in France 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

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$\beta^{A\text{-}T87Q}$-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. We expect to submit an IND with the FDA in 2014 to evaluate LentiGlobin in patients with SCD.

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	5,941,176 shares
Common stock to be outstanding after this offering	22,810,664 shares
Option to purchase additional shares	The underwriters have an option for a period of 30 days to purchase up to 891,176 additional shares of our common stock.
Use of proceeds	We estimate that the net proceeds from this offering will be approximately $90.9 million, or approximately $105.0 million if the underwriters exercise their option to purchase additional shares in full, based on the initial public offering price of $17.00 per share, after deducting the 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.
Nasdaq Global Select Market symbol	BLUE

The number of shares of common stock to be outstanding after this offering is based on 480,978 shares of common stock outstanding as of May 31, 2013 (which includes 116,612 shares of unvested restricted stock subject to repurchase by us) and 16,388,510 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:

- 3,839,025 shares of common stock issuable upon the exercise of outstanding stock options as of May 31, 2013 having a weighted-average exercise price of $3.69 per share;

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440,346 shares of common stock issuable upon the exercise of outstanding warrants as of May 31, 2013 having a weighted-average exercise price of $9.24 per share;

358,869 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

955,000 shares of common stock reserved for issuance (including the above-referenced shares reserved for issuance under our 2010 Stock Option and Grant Plan) 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 16,388,510 shares of common stock upon the closing 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 May 31, 2013; and

reflects a one-for-18.967 reverse stock split of our common stock that became effective on June 3, 2013.

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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	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)	$ (171.59)	$ (13.79)	$ (28.49)	$ (19.94)
Weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted	120	262	223	328
Pro forma net loss per share applicable to common stockholders basic and diluted (unaudited)(1)		$ (1.81)		$ (0.39)
Pro forma weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted (unaudited)		13,112		16,717

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(in thousands)	Actual	Pro Forma(2)	As of March 31, 2013 Pro Forma Adjusted (3)
		(unaudited)	
Consolidated balance sheet data:			
Cash and cash equivalents	$ 131,836	$ 131,836	$ 222,766
Working capital	105,390	105,390	196,320
Total assets	137,459	137,459	228,389
Preferred stock	122,177		
Common stock and additional paid-in capital	15,966	138,399	229,329
Total stockholders (deficit) equity	(61,595)	58,501	149,431

(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, based on the initial public offering price of $17.00 per share, after deducting underwriting discounts and commissions and 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 $90.9 million, based on the initial public offering price of $17.00 per share, after deducting underwriting discounts and commissions and estimated 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. It has been estimated that about 1.5% (80 to 90 million people) of the global population are carriers of ß-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. According to Thalassemia International Federation, about 288,000 patients with ß-thalassemia major are alive and registered as receiving regular treatment around the world, of which it is estimated that about 15,000 live in the United States and Europe. The global incidence of SCD is estimated to be 250,000-300,000 births annually with a global prevalence estimated to be about 20-25 million. The worldwide incidence rate for adrenoleukodystrophy, or ALD, the superset of CCALD, is approximately one in 20,000 newborn males. CCALD accounts for about 30-40% of patients diagnosed with ALD. Further, because newborn screening for CCALD is not widely adopted, and it can be difficult to diagnose CCALD in the absence of a genetic screen, we may have difficulty finding patients who are eligible to participate in our study. The eligibility criteria of our clinical studies will further limit the pool of available study participants. Additionally, the process of finding and diagnosing patients may prove costly. Finally, our treatment process requires that the patient be near one of our transduction facilities, as the hematopoietic stem cells, or HSCs, have limited viability following harvest and cannot be transported long distances.

Our current product candidates are being developed to treat rare conditions. 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

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

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

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

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

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

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

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

We are highly dependent on principal members of our executive team and key employees 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, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical studies may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

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

As of 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

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

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 Select Market have imposed various requirements on public companies. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. 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

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

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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 62.6% of our voting stock and, upon closing of this offering, that same group will beneficially own approximately 46.8% 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 $10.41 per share, based on the initial public offering price of $17.00 per share 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 41.1% of the total amount invested by stockholders since our inception, but will own only approximately 26.0% 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 3,652,786 shares of our common stock at a weighted average exercise price of $3.46 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 May 31, 2013, upon the closing of this offering, we will have outstanding a total of 22,810,664 shares of common stock, assuming no exercise of the underwriters option to purchase additional shares. Of these shares, as of the date of this prospectus, approximately 6.0 million 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, based upon the number of shares of common stock, on an as-converted basis, outstanding as of May 31, 2013, up to an additional 16.8 million shares of common stock will be eligible for sale in the public market, 14.6 million 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 May 31, 2013, 4,638,240 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 16.3 million shares of our common stock 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 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors 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,

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

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 5,941,176 shares of common stock in this offering will be approximately $90.9 million based on the initial public offering price of $17.00 per share, after deducting 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 $105.0 million after deducting 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 $11.8 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 $12.7 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 $2.5 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.

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 16,388,510 shares of common stock and the reclassification of our outstanding warrants to purchase shares of preferred stock to common stock, in each case upon the closing 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 underwriting discounts and commissions and estimated offering expenses payable by us, based on the initial public offering price of $17.00 per share.

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.

(in thousands, except per share data)	As of March 31, 2013		
	Actual	Pro forma	Pro forma as adjusted
		(unaudited)	
Cash and cash equivalents	$ 131,836	$ 131,836	$ 222,766
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		
Preferred Stock, $0.01 par value; 5,000 shares authorized and no shares issued and outstanding at March 31, 2013, pro forma and pro forma as adjusted			
Common stock, $0.01 par value; 21,511 shares authorized, actual and pro forma; 348 shares issued and outstanding at March 31, 2013, and 16,737 shares issued and outstanding pro forma(1); 125,000 shares authorized and 22,678 shares issued and outstanding, pro forma as adjusted	3	167	227
Additional paid-in capital	15,963	138,232	229,102
Accumulated deficit	(79,898)	(79,898)	(79,898)
Total stockholders (deficit) equity	(61,595)	58,501	149,431
Total capitalization	$ 58,501	$ 58,501	$ 149,431

(1) Excludes 132 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:

- 3,652,786 shares of common stock issuable upon the exercise of outstanding stock options having a weighted-average exercise price of $3.46 per share;
- 440,346 shares of common stock issuable upon the exercise of outstanding warrants having a weighted-average exercise price of $9.24 per share;
- 546,030 shares of common stock reserved for issuance pursuant to future equity awards under our 2010 Stock Option and Grant Plan; and
- 955,000 shares of common stock reserved for issuance (including the above-referenced shares reserved for issuance under our 2010 Stock Option and Grant Plan) 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 $3.50 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, upon the closing 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 $(177.00) 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 132,130 shares of unvested restricted stock subject to repurchase by us). After giving effect to (1) the conversion of all of our preferred stock into 16,388,510 shares of common stock upon the closing of this offering and (2) the sale of 5,941,176 shares of common stock in this offering, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, based on the initial public offering price of $17.00 per share, our pro forma as adjusted net tangible book value as of March 31, 2013 would have been approximately $149.4 million, or approximately $6.59 per share of common stock. This represents an immediate increase in pro forma as adjusted net tangible book value of $3.09 per share to our existing stockholders and an immediate dilution of $10.41 per share to investors participating in this offering. The following table illustrates this per share dilution:

Initial public offering price per share		$ 17.00
Historical net tangible book value per share as of March 31, 2013	$ (177.00)	
Increase attributable to the conversion of outstanding preferred stock and reclassification of preferred stock warrants	180.50	
Pro forma net tangible book value per share as of March 31, 2013	3.50	
Increase in net tangible book value per share attributable to new investors	3.09	
Pro forma net tangible book value per share after this offering		6.59
Dilution per share to new investors		$ 10.41

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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 16,388,510 shares of common stock prior to the completion of this offering) and by investors participating in this offering, after deducting underwriting discounts and commissions and estimated offering expenses, based on the initial public offering price of $17.00 per share.

	Shares purchased		Total consideration		Average price per share
	Number	Percent	Amount	Percent	
Existing stockholders	16,868,566	74.0%	$ 144,875,241	58.9%	$ 8.59
New investors	5,941,176	26.0%	100,999,992	41.1%	$ 17.00
Total	22,809,742	100.0%	$ 245,875,233	100.0%	$ 10.78

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:

- 3,652,786 shares of common stock issuable upon the exercise of outstanding stock options having a weighted-average exercise price of $3.46 per share;
- 440,346 shares of common stock issuable upon the exercise of outstanding warrants having a weighted-average exercise price of $9.24 per share;
- 546,030 shares of common stock reserved for issuance pursuant to future equity awards under our 2010 Stock Option and Grant Plan; and
- 955,000 shares of common stock reserved for issuance (including the above-referenced shares reserved for issuance under our 2010 Stock Option and Grant Plan) 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 March 31, 2013 will increase to $163.5 million, or $6.94 per share, representing an increase to existing stockholders of $3.44 per share, and there will be an immediate dilution of $10.06 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)	$ (171.59)	$ (13.79)	$ (28.49)	$ (19.94)
Weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted	120	262	223	328
Pro forma net loss per share applicable to common stockholders basic and diluted (unaudited)(1)		$ (1.81)		$ (0.39)
Pro forma weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted (unaudited)		13,112		16,717

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(in thousands)	Actual	As of March 31, 2013 Pro Forma Pro Forma(2)	Pro Forma Adjusted (3)
		(unaudited)	
Consolidated balance sheet data:			
Cash and cash equivalents	$ 131,836	$ 131,836	$ 222,766
Working capital	105,390	105,390	196,320
Total assets	137,459	137,459	228,389
Preferred stock	122,177		
Common stock and additional paid-in capital	15,966	138,399	229,329
Total stockholders (deficit) equity	(61,595)	58,501	149,431

(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, based on the initial public offering price of $17.00 per share, after deducting underwriting discounts and commissions and 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 a Phase I/II clinical study in the United States and have initiated a Phase I/II clinical study in 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 half 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 have initiated 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 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

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	623,087	$ 2.09	$ 2.09
7/13/2011	Restricted stock award	14,390	2.09	2.09
10/25/2011	Option	312,121	2.09	2.09
1/8/2012	Option	189,344	2.09	2.09
2/10/2012	Option	65,172	2.09	2.09
4/13/2012	Option	157,239	2.09	2.09
6/4/2012	Option	213,257	2.09	2.09
10/9/2012	Option	160,483	2.66	2.66
1/16/2013	Option	1,399,963	5.50	5.50
2/4/2013	Option	68,012	5.50	5.50

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 price of $7.12287 per share of common stock issuable upon the conversion of Series C preferred stock sold in April 2011, which financing was led by an unrelated investor that had not previously invested in our Company. Given the proximity to the 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 $2.09 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)	$ 3.22

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 $2.09 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)	$ 2.79

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 price of $9.45126 per share of common stock issuable upon the conversion of Series D preferred stock sold 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 unrelated investors, we believe the per share issuance price of the Series D

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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 $2.66 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)	$ 5.88	$ 2.85

The estimated per share fair value of our common stock calculated in our valuation as of July 23, 2012 of $2.66 per share increased from the April 15, 2012 valuation of $2.09 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 our 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 $5.50 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)	$ 9.10	$ 4.17

The estimated per share fair value of our common stock calculated in our valuation as of December 31, 2012 of $5.50 per share increased significantly from the July 23, 2012 valuation of $2.66 per share. This is primarily due to the following factors:

- potential partnership with a leading pharmaceutical company that would extend our platform into oncology indications;
- 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
- award of a $9.3 million grant 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 $8.16 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)	$ 10.62	$ 5.12

The estimated per share fair value of our common stock calculated in our valuation as of March 31, 2013 of $8.16 per share increased from the December 31, 2012 valuation of $5.50 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

The initial public offering price of $17.00 per share was determined as a result of negotiations between us and the underwriters. In comparison, our estimate of the fair value of our common stock was $8.16 per share as of March 31, 2013. We note that, as is typical in IPOs, the initial public offering price 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 price 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 initial public offering price reflects a significant increase over the estimated valuation as of March 31, 2013 of $8.16 per share. Investors should be aware of this difference and recognize that the initial public offering price 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 contemporaneous valuation prepared as of March 31, 2013 contained multiple liquidity scenarios, including an initial public offering with an anticipated completion date of August 31, 2013 to which we assigned a probability weighting of 70%. However, the consideration of different scenarios accounts for some but not all of the difference between the initial public offering price and the valuation as of March 31, 2013.
- Our receipt in late April of notice that the IND for our Lenti-D program in the United States is now active.
- Improved capital market conditions for companies in our industry, as evidenced by a recent increase in the number of public offerings by such companies and in the initial public offering valuations of such companies compared to the valuations in their most recent pre-IPO equity financing.
- The initial public offering price 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. Our March 31, 2013 valuation included an illiquidity discount of 10%.
- In the public markets we believe there are investors who may apply more qualitative and subjective valuation criteria to certain of our clinical assets than the valuation methods

applied in our valuations, although there can be no assurance that this will in fact be the case. As described above, as a private company we used a more quantitative methodology to determine the fair value of our common stock and this methodology differs from the methodology used to determine the initial public offering price. The initial public offering price was not derived using a formal determination of fair value, but rather was determined by negotiation between us and the underwriters. In particular, the estimate of fair value of our common stock as of March 31, 2013 was not a factor in setting the initial public offering price.

The price that investors are willing to pay in this offering 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.

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.

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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.

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.

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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)

Revenue. Revenue was $1.1 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.

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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:

- $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.

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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 half 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.

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.

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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

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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;

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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.

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 a licensed product, provided that the royalty to Stanford is not less than a specified percentage that is less than one percent. We are required to pay Stanford an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.

Under a license agreement with the Massachusetts Institute of Technology, or MIT, pursuant to which we license various patents, we will be required to make a payment of $0.1 million based upon a regulatory filing milestone. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property by us or our sublicensees. The royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one percent. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the mid-single digits to low double digits. We are required to pay MIT an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.

Under a license agreement with Research Development Foundation pursuant to which we license patents that involve lentiviral vectors, we will be required to make payments of $1.0 million based upon a regulatory milestone for each product covered by the in-licensed intellectual property. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which is reduced by half if during the ten year following first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.

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

On June 3, 2013, we entered into a new nine-year building lease for approximately 43,600 square feet of space in Cambridge, Massachusetts, commencing on the earlier of the substantial completion of our build-out work or January 1, 2014. The lease has monthly lease payments of $0.2 million for the first 12 months with annual rent escalations thereafter and provides a rent abatement of $0.2 million per month for the first six months. The total operating lease obligation of the noncancellable term of this agreement is $24.2 million. In addition, the lease

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provides a contribution from the landlord towards the initial build-out of the space of up to $6.5 million. We have the option to extend this lease by an additional five years. In accordance with the lease, we entered into a cash-collateralized irrevocable standby letter of credit in the amount of $1.3 million, naming the landlord as beneficiary. Our current building lease in Cambridge, Massachusetts, expires on March 31, 2015. We plan to relocate to the new space prior to its expiration.

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, a Phase I/II clinical study in the United States and have initiated a Phase I/II clinical study in 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

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 have initiated an extension of this study under a revised protocol for LentiGlobin, which we refer to as the HGB-205 Study. 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. We expect to submit an IND with the FDA in 2014 to evaluate LentiGlobin in patients with SCD.

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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 worldwide incidence rate for ALD is approximately one in 20,000 newborn males.

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

CCALD (Childhood cerebral adrenoleukodystrophy): The most severe form of ALD is CCALD. CCALD accounts for about 30-40% of patients diagnosed with ALD and presents in young boys. CCALD is characterized by progressive destruction of myelin, leading to severe loss of neurological function and eventual death. In boys affected by CCALD, learning and behavioral problems are often observed in mid-childhood between the ages of 3 and 15 years (median age 7). In the absence of intervention, boys affected by CCALD typically experience rapid degeneration into vegetative state, and ultimately death within a decade of diagnosis.

AMN (Adrenomyeloneuropathy): AMN which typically develops in adults aged 21 years and older, is the most common neurological form of ALD, accounting for 40-45% of all patients diagnosed with ALD. All patients with AMN present with more slowly progressive symptoms resulting from (non-inflammatory) disruption of the axons (which are a fundamental component of the central nervous system that allows nerve signals to be transmitted) in the spinal cord. Approximately 40% of these patients have or will develop cerebral disease similar to CCALD, with varying degrees of associated inflammation.

ACALD (Adult Cerebral ALD): ACALD typically develops in males aged 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

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

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

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

Limitations of current treatment options

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

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

Our LentiGlobin product candidate

We are developing our LentiGlobin product candidate as a potential one-time treatment for both ß-thalassemia 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 have initiated our HGB-205 clinical study, and we expect to initiate our HGB-204 clinical study in mid-2013. We expect to have preliminary, interim data from one or both of these clinical studies in late 2014, although there can be no assurance this will be the case.

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

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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 initiated 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

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 in patients with ß-thalassemia. 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. We expect to submit an IND with the FDA in 2014 to evaluate LentiGlobin in patients with SCD.

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

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 clinical, regulatory and commercial milestones, is $225 million, and the royalties payable to us range from the mid-single digits to mid-teens. The royalties payable to us are subject to certain reductions, including for any royalty payments required to be made by Celgene to acquire patent rights, with an aggregate minimum floor. Celgene will assume certain development obligations and must report on their progress in achieving these milestones on a quarterly basis. If we do elect to co-develop and co-promote the product candidate within the United States, we would share equally in all costs relating to developing, commercializing and manufacturing the product candidate within the United States and we would share equally in the United States profits.

Celgene will be solely responsible for all costs and expenses of manufacturing and supplying any optioned product candidates. Subject to customary back-up supply rights granted to Celgene, we have the sole right to manufacture or have manufactured supplies of vectors and associated payloads manufactured for incorporation into the optioned product candidate. 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 a specified period following completion of a pivotal study for that product candidate.

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

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

Baylor College of Medicine

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

Call Option and Target Antigen License

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.

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 curre