bluebird bio, Inc.
Form S-1/A
June 04, 2013
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As filed with the Securities and Exchange Commission on June 4, 2013

Registration No. 333-188605

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Amendment No. 2

to

FORM S-1

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

bluebird bio, Inc.

(Exact name of registrant as specified in its charter)

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

840 Memorial Drive, 4th Floor

Cambridge, MA 02139

(617) 491-5601

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

Nick Leschly

President and Chief Executive Officer

bluebird bio, Inc.

840 Memorial Drive, 4th Floor

Cambridge, MA 02139

(617) 491-5601

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

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

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

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

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

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

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

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

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be Registered(1)	Proposed Maximum Offering Price Per Share(2)	Proposed Maximum Aggregate Offering Price(2)	Amount of Registration Fee(3)
Common stock, $0.01 par value	5,750,000	$16.00	$92,000,000.00	$12,548.80

(1) Includes 750,000 shares which the underwriters have the option to purchase.

(2) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(a) under the Securities Act.

(3) Of this amount, $11,764.50 was previously paid in connection with the initial filing of this Registration Statement on May 14, 2013.

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

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

Subject to completion, dated June 4, 2013

Prospectus

5,000,000 shares

Common stock

This is an initial public offering of common stock by bluebird bio, Inc. We are selling 5,000,000 shares of common stock. The estimated initial public offering price is between $14.00 and $16.00 per share.

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

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

	Per share	Total
Initial public offering price	$	$
Underwriting discounts and commissions(1)	$	$
Proceeds to bluebird bio, before expenses	$	$

(1) The underwriters will receive compensation in addition to the underwriting discount. See Underwriting beginning on page 192.

We have granted the underwriters an option for a period of 30 days to purchase up to 750,000 additional shares of common stock.

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

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

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

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

Cowen and Company

Canaccord Genuity

Wedbush PacGrow Life Sciences

, 2013

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

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

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Prospectus summary

Overview

We are a clinical-stage biotechnology company focused on transforming the lives of patients with severe genetic and orphan diseases using gene therapy. Many diseases have a genetic aspect whereby a mutated gene linked to a disease is passed down from generation to generation. Genes produce proteins that perform a vast array of functions within all living organisms, through a process called gene expression. A mutation, or alteration, in the gene or in sequences that control the expression of that gene can cause proteins to be produced aberrantly in the cell, which can cause disease. Gene therapy seeks to introduce a functional copy of the defective gene into a patient s own cells, a process called gene transfer. Gene therapy thereby has the potential to change the way these patients are treated by correcting the underlying genetic defect that is the *cause* of their disease, rather than offering solutions that only address their *symptoms*. Accordingly, we believe gene therapy has the potential to provide transformative disease modifying effects with life-long clinical benefits based on a single therapeutic administration.

In the gene transfer process, a functional gene is delivered and incorporated into a patient s cells through a delivery system called a vector, which are most commonly based on naturally-occurring viruses that have been modified to take advantage of the virus natural ability to introduce genes into cells. However, unlike naturally-occurring viruses, which replicate following infection of a target cell and have the capacity to infect new cells, viral vectors are modified to be non-replicating by deleting that portion of the viral genome responsible for replication. Gene transfer using a viral vector is called transduction and the resulting gene-modified cells are described as transduced cells.

A growing body of gene therapy-based clinical data, the establishment of regulatory guidelines to govern the development and approval of gene therapy products and increased investment from the biopharmaceutical industry suggest that the time is now for gene therapy to emerge as an important new therapeutic modality for patients with significant unmet medical need. We believe we are particularly well-positioned to drive the continued advancement of gene therapy technology for the treatment of severe genetic and orphan diseases. We have assembled extensive expertise in viral vector design, manufacturing and gene transfer, a broad intellectual property estate, an experienced management team and a world-class group of scientific advisors and key opinion leaders. We refer to our viral vector and gene transfer technology and know-how as our gene therapy platform.

We and our scientific collaborators have generated what we believe is human proof-of-concept data for our gene therapy platform in two underserved diseases, each of which has been granted orphan drug status by U.S. and European regulatory authorities. We expect to initiate in late 2013 a Phase II/III clinical study of our most advanced product candidate, Lenti-D, to evaluate its safety and efficacy in subjects with childhood cerebral adrenoleukodystrophy, or CCALD, a rare, hereditary neurological disorder affecting young boys that is often fatal. We also expect to initiate in mid-2013 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	5,000,000 shares
Common stock to be outstanding after this offering	21,869,488 shares
Option to purchase additional shares	The underwriters have an option for a period of 30 days to purchase up to 750,000 additional shares of our common stock.
Use of proceeds	We estimate that the net proceeds from this offering will be approximately $66.8 million, or approximately $77.2 million if the underwriters exercise their option to purchase additional shares in full, at an assumed initial public offering price of $15.00 per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering to fund direct research and development expenses for our Phase II/III clinical study for our Lenti-D product candidate and our Phase I/II clinical studies for our LentiGlobin product candidate. We intend to use remaining amounts for general and administrative expenses (including personnel-related costs), potential future development programs, early-stage research and development, capital expenditures and working capital and other general corporate purposes. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary gene therapy businesses, technologies, products or assets. See Use of proceeds.
Risk factors	You should read the Risk factors section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Proposed Nasdaq Global Market symbol	BLUE

The number of shares of common stock to be outstanding after this offering is based on 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	As of March 31, 2013 Pro Forma(2)	Pro Forma Adjusted (3)(4)
		(unaudited)	
Consolidated balance sheet data:			
Cash and cash equivalents	$ 131,836	$ 131,836	$ 198,586
Working capital	105,390	105,390	172,140
Total assets	137,459	137,459	204,209
Preferred stock	122,177		
Common stock and additional paid-in capital	15,966	138,399	205,149
Total stockholders (deficit) equity	(61,595)	58,501	125,251

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

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

(3) Pro forma as adjusted to further reflect the sale of shares of our common stock offered in this offering, assuming an initial public offering price of $15.00 per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

(4) A $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per share, the midpoint of the price range set forth on the cover of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash and cash equivalents and total stockholders (deficit) equity by approximately $4.7 million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. A 1,000,000 share increase in the number of shares offered by us together with a concomitant $1.00 increase in the assumed initial public offering price of $15.00 per share, the midpoint of the price range set forth on the cover of this prospectus, would increase each of cash and cash equivalents and total stockholders (deficit) equity by approximately $19.5 million after deducting underwriting discounts and commissions and any estimated offering expenses payable by us. Conversely, a 1,000,000 share decrease in the number of shares offered by us together with a concomitant $1.00 decrease in the assumed initial public offering price of $15.00 per share, the midpoint of the price range set forth on the cover of this prospectus, would decrease each of cash and cash equivalents and total stockholders (deficit) equity by approximately $17.7 million after deducting underwriting discounts and commissions and any estimated offering expenses payable by us.

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Risk factors

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

Risks related to our financial condition and capital requirements

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

We are a clinical-stage biotechnology company, and we have not yet generated significant revenues. We have incurred net losses in each year since our inception in 1992, including net losses of $15.6 million and $23.7 million for the years ended December 31, 2011 and 2012, respectively, and $6.5 million for the three months ended March 31, 2013. As of March 31, 2013, we had an accumulated deficit of $79.9 million.

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

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

- continue our research and preclinical and clinical development of our product candidates;
- expand the scope of our current clinical studies for our product candidates;
- initiate additional preclinical, clinical or other studies for our product candidates, including under our collaboration agreement with Celgene Corporation;
- further develop the manufacturing process for our vectors or our product candidates;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;

seek to identify and validate additional product candidates;

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- acquire or in-license other product candidates and technologies;
- make milestone or other payments under any in-license agreements;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel;
- create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above.

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

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

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

- completing research and preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- developing a sustainable, scalable, reproducible, and transferable manufacturing process for our vectors and product candidates;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for our product candidates, if approved;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval, either by collaborating with a partner or, if launched independently, by establishing a sales force, marketing and distribution infrastructure;
- obtaining market acceptance of our product candidates and gene therapy as a viable treatment option;
- addressing any competing technological and market developments;

implementing additional internal systems and infrastructure, as needed;

identifying and validating new gene therapy product candidates;

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

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

attracting, hiring and retaining qualified personnel.

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

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

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

As of March 31, 2013, our cash and cash equivalents were $131.8 million. We estimate that the net proceeds from this offering will be approximately $66.8 million, assuming an initial public offering price of $15.00 per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting estimated underwriting discounts and commissions and offering expenses payable by us. We expect that the net proceeds from this offering and our existing cash and cash equivalents will be sufficient to fund our current operations through at least the end of 2015. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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

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ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

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

Risks related to the discovery and development of our product candidates

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

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

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

Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. For example, the FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical studies conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health, or the NIH, are also subject to review by the NIH Office of Biotechnology Activities Recombinant DNA Advisory Committee, or the RAC. Although the FDA decides whether individual gene therapy protocols may proceed, the RAC review process can impede the initiation of a clinical study, even if the FDA has reviewed the study and approved its

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initiation. Conversely, the FDA can put an investigational new drug application, or IND, on clinical hold even if the RAC has provided a favorable review. Also, before a clinical study can begin at an NIH-funded institution, that institution s institutional review board, or IRB, and its Institutional Biosafety Committee will have to review the proposed clinical study to assess the safety of the study. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other regulatory bodies to change the requirements for approval of any of our product candidates.

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

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

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

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

- severity of the disease under investigation;
- design of the study protocol;
- size of the patient population;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study;
- proximity and availability of clinical study sites for prospective patients;
- availability of competing therapies and clinical studies;
- efforts to facilitate timely enrollment in clinical studies;

patient referral practices of physicians; and

ability to monitor patients adequately during and after treatment.

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In particular, each of the conditions for which we plan to evaluate our current product candidates are rare genetic disorders with limited patient pools from which to draw for clinical studies. 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

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applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

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

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

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. An alternative manufacturer would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

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

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

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

We and our CROs are required to comply with the FDA s GCPs for conducting, recording and reporting the results of IND-enabling studies and clinical studies to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical study participants are protected. The FDA enforces these GCPs through periodic

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

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

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

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

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

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic