

bluebird bio, Inc.
 Form 424B7
 July 30, 2014
Table of Contents

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered	Proposed Maximum Offering Price Per Unit(1)	Proposed Maximum Aggregate Offering Price(1)	Amount of Registration Fee(2)
Common Stock, par value \$0.01 per share	504,903	\$33.47	\$16,899,103	\$2,176.60

- (1) Estimated solely for purposes of calculating the registration fee pursuant to Rule 457(c) of the Securities Act of 1933, as amended (the Securities Act), based on the market value of bluebird bio, Inc. common stock being registered, as established by the average of the high and low prices of bluebird bio, Inc. common stock as reported on the NASDAQ Global Select Market on July 29, 2014, which was \$33.47.
- (2) Calculated in accordance with Rule 456(b) and 457(r) of the Securities Act.

Table of Contents

Filed Pursuant to Rule 424(b)(7)

Registration No.: 333-197192

PROSPECTUS SUPPLEMENT

(To Prospectus dated July 2, 2014)

Common Stock

This prospectus supplement relates to the possible resale from time to time of up to 504,903 shares of our common stock, par value \$0.01 per share, by the persons named in this prospectus supplement under the caption **Selling Stockholders**. The prices at which such selling stockholders may dispose of their shares will be determined by the selling stockholders or their transferees. We will not receive proceeds from any sale of shares of common stock by the selling stockholders, but we have agreed to pay certain registration expenses relating to such shares of common stock.

The selling stockholders from time to time may offer and sell the shares of common stock held directly by them or through underwriters, broker-dealers or agents, who may receive compensation in the form of discounts, commissions or concessions. For further information regarding the possible methods by which shares of common stock may be distributed, see **Plan of Distribution** beginning on page S-9 of this prospectus supplement.

Our common stock is traded on the NASDAQ Global Select Market under the symbol **BLUE**. On July 29, 2014, the reported closing price per share of our common stock was \$33.87.

Investing in our common stock involves risks. See Risk Factors on page S-4 of this prospectus supplement and the risk factors described in the other documents incorporated herein by reference.

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

The date of this prospectus supplement is July 30, 2014.

Table of Contents

TABLE OF CONTENTS

	Page
<u>ABOUT THIS PROSPECTUS SUPPLEMENT</u>	S-1
<u>PROSPECTUS SUPPLEMENT SUMMARY</u>	S-2
<u>RISK FACTORS</u>	S-4
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	S-5
<u>USE OF PROCEEDS</u>	S-7
<u>SELLING STOCKHOLDERS</u>	S-8
<u>PLAN OF DISTRIBUTION</u>	S-9
<u>DESCRIPTION OF CAPITAL STOCK</u>	S-10
<u>LEGAL MATTERS</u>	S-14
<u>EXPERTS</u>	S-14
<u>WHERE YOU CAN FIND ADDITIONAL INFORMATION</u>	S-15
<u>ABOUT THIS PROSPECTUS</u>	1
<u>WHERE YOU CAN FIND ADDITIONAL INFORMATION</u>	3
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	4
<u>CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS</u>	5
<u>RISK FACTORS</u>	6
<u>ABOUT THE COMPANY</u>	7
<u>DESCRIPTION OF SECURITIES</u>	8
<u>RATIO OF EARNINGS TO FIXED CHARGES</u>	10
<u>USE OF PROCEEDS</u>	11
<u>SELLING STOCKHOLDERS</u>	12
<u>PLAN OF DISTRIBUTION</u>	13
<u>LEGAL MATTERS</u>	15
<u>EXPERTS</u>	15

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is part of the registration statement that we filed with the Securities and Exchange Commission, or SEC, using a shelf registration process and consists of two parts. The first part is this prospectus supplement, including the documents incorporated by reference, which describes the specific terms of this offering. The second part, the accompanying prospectus, including the documents incorporated by reference, gives more general information, some of which does not apply to this offering. Generally, when we refer to the prospectus, we are referring to both parts combined. This prospectus supplement may add to, update or change information in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement or the accompanying prospectus.

If information in this prospectus supplement is inconsistent with the accompanying prospectus or with any document incorporated by reference that was filed with the SEC before the date of this prospectus supplement, you should rely on this prospectus supplement. This prospectus supplement, the accompanying prospectus and the documents incorporated into each by reference include important information about us, the selling stockholders, the common stock being offered and other information you should know before investing in our common stock. You should also read and consider information in the documents we have referred you to in the sections of this prospectus supplement and the accompanying prospectus entitled *Where You Can Find More Information* and *Incorporation of Certain Information by Reference*.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We and the selling stockholders have not authorized anyone to provide you with information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus. We and the selling stockholders take no responsibility for, and can provide no assurances as to the reliability of, any other information that others may give you. The selling stockholders are not offering to sell these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus is accurate as of any date other than as of the date of this prospectus supplement or the accompanying prospectus, as the case may be, or in the case of the documents incorporated by reference, the date of such documents regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sale of our common shares. Our business, financial condition, liquidity, results of operations and prospects may have changed since those dates.

All references in this prospectus supplement or the accompanying prospectus to bluebird bio, the Company, we, us, our mean bluebird bio, Inc. and our subsidiaries, unless we state otherwise or the context otherwise requires. 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. This prospectus supplement and the information incorporated herein by reference contain references to trademarks, service marks and trade names owned by us or other companies. Solely for convenience, trademarks, service marks and trade names referred to in this prospectus supplement and the information incorporated herein, 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, service marks and

trade names. We do not intend our use or display of other companies' trade names, service marks or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement or any related free writing prospectus are the property of their respective owners.

S-1

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary may not contain all the information that you should consider before investing in our securities. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under Risk Factors beginning on page S-4 of this prospectus supplement, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision. This prospectus supplement may add to, update or change information in the accompanying prospectus.

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

We also are conducting Phase I/II clinical studies in both the United States and Europe of our next most advanced product candidate, LentiGlobin, to evaluate its safety and efficacy in subjects with β -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 December 2013, we announced that the first subject with β -thalassemia major had been treated in our European study (the HGB-205 Study). In March 2014, we announced that the first subject with β -thalassemia major had been treated in our study in the United States (the Northstar Study). We presented initial results from the European clinical study of β -thalassemia major at the European Hematology Association Congress in Milan, Italy in June 2014.

We also have an active investigational new drug application in the United States for a Phase I clinical study to evaluate the safety and efficacy of LentiGlobin in subjects with severe SCD (the HGB-206 Study). We are planning to treat the first SCD patient with our LentiGlobin product candidate in 2014. Orphan drug status has been granted for LentiGlobin for the treatment of SCD by U.S. regulatory authorities.

In March 2013, we announced a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel, disease-altering gene therapies in oncology. The collaboration focuses on applying gene therapy technology to genetically modify a patient's own T cells to target and destroy cancer cells. Such modified T cells, called chimeric antigen receptor, or CAR, T cells have been shown 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.

Edgar Filing: bluebird bio, Inc. - Form 424B7

Our mailing address and executive offices are located at 150 Second Street, Cambridge, Massachusetts and our telephone number at that address is (339) 499-9300. We maintain an Internet website at the following address: www.bluebirdbio.com. The information on, or that can be accessed through, our website does not constitute part of this prospectus supplement or the accompanying prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock.

S-2

Table of Contents

The Offering

Issuer	bluebird bio, Inc.
Selling Stockholders	For information concerning the shares of common stock that may be offered from time to time by the selling stockholders pursuant to this prospectus supplement, see the Selling Stockholders section of this prospectus supplement.
Common stock offered by the Selling Stockholders	504,903 shares
NASDAQ Global Select Market Symbol	BLUE
Use of proceeds	We will not receive any of the proceeds from any sales of shares of common stock by the selling stockholders. See the Use of Proceeds section of this prospectus supplement.
Risk Factors	See the Risk Factors section of this prospectus supplement for a discussion of factors you should consider carefully when making an investment decision.

Table of Contents**RISK FACTORS**

*Investing in our securities involves a high degree of risk. In addition to the other information contained in this prospectus supplement to the accompanying prospectus and in the documents we incorporate by reference, you should carefully consider the risks discussed below and under the heading **Risk Factors** in our Annual Report on Form 10-K for the fiscal year ended December 31, 2013, filed with the SEC on March 5, 2014, and in our Quarterly Report on Form 10-Q for the quarter ended March 31, 2014, filed with the SEC on May 13, 2014, as updated by our Quarterly Reports on Form 10-Q, our Annual Reports on Form 10-K, and our other filings with the SEC filed after the date of this prospectus supplement, before making a decision about investing in our securities. The risks and uncertainties discussed below and in our Annual Report on Form 10-K for the fiscal year ended December 31, 2013 and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2014 are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also harm our business. If any of these risks occur, our business, financial condition and operating results could be harmed, the trading price of our common stock could decline and you could lose part or all of your investment.*

Risks Related to Our Business

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

On June 14, 2014, we released initial clinical data on two subjects from our HGB-205 Study of our LentiGlobin BB305 product candidate in beta-thalassemia major subjects at the 19th Annual Congress of the European Hematology Association in Milan, Italy. Although the initial clinical data on these two subjects are encouraging, the data are preliminary in nature, based on limited periods of time since patient infusion, and the HGB-205 Study is not complete. The data may not continue to be positive for these subjects or be positive for any future subjects in this study. In addition, positive data may not be repeated or observed in ongoing or future studies involving our LentiGlobin product candidate, including the HGB-205 Study, the Northstar Study or the HGB-206 Study in sickle cell disease. There can be no assurance that any of these studies will be successful or support further clinical advancement of this product candidate. There is a high failure rate for drugs and biologics proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies, and any such setbacks in our clinical development could have a material adverse effect on our business and operating results.

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

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

S-4

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the information incorporated herein by reference herein and therein contain statements that are not historical facts and are considered forward-looking within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These forward-looking statements contain projections of our future results of operations or of our financial position or state other forward-looking information. In some cases you can identify these statements by forward-looking words such as anticipate, believe, could, continue, estimate, expect, intend, may, plan, projected or the negative of such words or other similar words or phrases. We believe that it is important to communicate our future expectations to our investors. However, there may be events in the future that we are not able to accurately predict or control and that may cause our actual results to differ materially from the expectations we describe in our forward-looking statements.

Investors are cautioned not to unduly rely on forward-looking statements because they involve risks and uncertainties, and statements relate to future events or our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. 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;

our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act, or the JOBS Act;

developments relating to our competitors and our industry; and

other risks and uncertainties, including those listed under the caption **Risk Factors** below and in any documents incorporated by reference herein.

Table of Contents

Given these uncertainties, readers should not place undue reliance on our forward-looking statements. These forward-looking statements speak only as of the date on which the statements were made and are not guarantees of future performance. Except as may be required by applicable law, we do not undertake or intend to update any forward-looking statements after the date of this prospectus or the respective dates of documents incorporated by reference herein or therein that include forward-looking statements.

S-6

Table of Contents

USE OF PROCEEDS

The proceeds from the disposition of the shares of common stock covered by this prospectus supplement will be received by the selling stockholders or their transferees. We will not receive any of the proceeds from the disposition of the shares by the selling stockholders or their transferees.

S-7

Table of Contents**SELLING STOCKHOLDERS**

On June 30, 2014, we entered into a Stock Purchase Agreement with Precision Genome Engineering, Inc. (Pregonen) and the selling stockholders (the Purchase Agreement), pursuant to which the selling stockholders sold, and we purchased, all of Pregonen s outstanding capital stock in exchange for, among other things, shares of our common stock. The Purchase Agreement provides that, among other things, the Company will file a shelf registration statement on Form S-3 and any applicable prospectus supplements thereto covering the resale of all shares of our common stock issued to the selling stockholders. This prospectus supplement is being filed pursuant to our obligations under the Purchase Agreement.

We are required to use our reasonable best efforts to maintain the effectiveness of the registration statement until all of these shares have been sold or may be sold freely without limitations or restrictions as to volume or manner of sale pursuant to Rule 144, or until the second anniversary of the effective date of the registration statement (if earlier).

The following table sets forth, subject to certain assumptions: (1) the name of each of the selling stockholders; (2) the number of shares of our common stock that are currently, or potentially will be, beneficially owned by each such selling stockholder (assuming that all shares held back by us pursuant to the Purchase Agreement are issued to the selling stockholders); (3) the maximum number of shares of our common stock being offered pursuant to this prospectus supplement; and (4) the number of shares of our common stock owned by each of the selling stockholders upon completion of this offering. Following the completion of this offering and assuming (i) the sale of all common stock offered hereunder and (ii) that no other shares are beneficially acquired by the selling stockholders, none of the selling stockholders listed below will own more than one percent (1%) of our outstanding common stock.

Beneficial ownership is determined in accordance with the rules of the SEC. Except as indicated by footnote and subject to community property laws where applicable, to our knowledge, each of the persons named in the table below has sole voting and investment power with respect to the shares of common stock shown as beneficially owned by each such person.

We have prepared this table using information furnished to us by or on behalf of the selling stockholders.

Name	Common Stock Owned Prior to this Offering	Common Stock Being Offered Pursuant to this Prospectus Supplement	Common Stock Owned Upon Completion of this Offering⁽¹⁾
Andrew Scharenberg	147,370	147,370	0
Jordan Jarjour ⁽²⁾	87,333	87,333	0
Rolf P. Scharenberg	84,572	84,572	0
Alexander (Sasha) Astrakhan ⁽²⁾	43,307	43,307	0
Raymond Monnat	40,077	40,077	0
Barry Stoddard	40,077	40,077	0
Laurie O. Beitz	20,821	20,821	0
Christian Burks	16,262	16,262	0
David Baker	10,573	10,573	0
John M. Fluke, Jr.	5,962	5,962	0

Edgar Filing: bluebird bio, Inc. - Form 424B7

Kyle Havens ⁽²⁾	4,390	4,390	0
Tomer Hertz	1,287	1,287	0
Wai Hang Leung ⁽²⁾	1,037	1,037	0
Jasdeep Mann ⁽²⁾	1,037	1,037	0
Michael Certo	634	634	0
Michael Mendez	164	164	0

- (1) Assumes each selling stockholder has sold all the shares of common stock shown as being offered by each selling stockholder pursuant to this prospectus supplement.
- (2) Selling stockholder became an employee of the Company upon the acquisition of Pregonen on June 30, 2014.

S-8

Table of Contents

PLAN OF DISTRIBUTION

We are registering the shares of common stock on behalf of the selling stockholders. The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. The selling stockholders may, from time to time, sell any or all of their shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. These sales may be at fixed or negotiated prices. The selling stockholders may use any one or more of the following methods when selling shares:

ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;

block trades in which the broker-dealer will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;

purchases by a broker-dealer as principal and resale by the broker-dealer for its account;

an exchange distribution in accordance with the rules of the applicable exchange;

privately negotiated transactions;

short sales;

through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;

broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;

pledges of the securities as security for any loan or obligation, including pledges to brokers or dealers who may from time to time effect sales or other distributions of the securities;

a combination of any such methods of sale; and

any other method permitted pursuant to applicable law.

The selling stockholders may also sell shares under Rule 144 under the Securities Act, if available, rather than under this prospectus supplement and accompanying prospectus.

Broker-dealers engaged by the selling stockholders may arrange for other brokers-dealers to participate in sales. Broker-dealers may receive commissions or discounts from the selling stockholders (or, if any broker-dealer acts as agent for the purchaser of shares, from the purchaser) in amounts to be negotiated. The selling stockholders do not expect these commissions and discounts to exceed what is customary in the types of transactions involved. Any profits on the resale of shares of common stock by a broker-dealer acting as principal might be deemed to be underwriting discounts or commissions under the Securities Act. Discounts, concessions, commissions and similar selling expenses, if any, attributable to the sale of shares will be borne by a selling stockholder. The selling stockholders may agree to indemnify any agent, dealer or broker-dealer that participates in transactions involving sales of the shares if liabilities are imposed on that person under the Securities Act.

To our knowledge, the selling stockholders have not entered into any agreements, understandings or arrangements with any underwriters or broker-dealers regarding the sale of their shares of common stock, nor is there an underwriter or coordinating broker acting in connection with a proposed sale of shares of common stock by any selling stockholder. If we are notified by any selling stockholder that any material arrangement has been entered into with a broker-dealer for the sale of shares of common stock, if required, we will file an amendment to this prospectus supplement. If the selling stockholders use this prospectus supplement and accompanying prospectus for any sale of the shares of common stock, they will be subject to the prospectus delivery requirements of the Securities Act.

Table of Contents

The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees or other successors in interest will be the selling beneficial owners for purposes of this prospectus supplement and accompanying prospectus and may sell the shares of common stock from time to time under this prospectus supplement and accompanying prospectus after we have filed an amendment to this prospectus supplement under Rule 424(b)(3) or other applicable provision of the Securities Act supplementing or amending the list of selling stockholders to include the transferee or other successors in interest as selling stockholders under this prospectus supplement.

The selling stockholders and any broker-dealers or agents that are involved in selling the shares of common stock may be deemed to be underwriters within the meaning of the Securities Act in connection with such sales. In such event, any commissions received by such broker-dealers or agents and any profit on the resale of the shares of common stock purchased by them may be deemed to be underwriting commissions or discounts under the Securities Act.

The selling stockholders and any other person participating in a distribution will be subject to the Exchange Act. The Exchange Act rules include, without limitation, Regulation M, which may limit the timing of purchases and sales of shares of our common stock by the selling stockholders and any such other person. In addition, Regulation M of the Exchange Act may restrict sales activity by a person engaged in the distribution of the shares for a period of up to five business days prior to the commencement of such distribution. This may affect the marketability of the shares of our common stock and the ability of any person or entity to engage in market-making activities with respect to shares of our common stock. We have informed the selling stockholders that the anti-manipulative provisions of Regulation M may apply to their sales in the market.

We are required to pay all fees and expenses incident to the registration of the shares of common stock. We cannot assure you that the selling stockholders will sell all or any portion of the securities offered hereby.

DESCRIPTION OF CAPITAL STOCK

This section describes the general terms of our common stock. For more detailed information, a holder of our common stock should refer to our certificate of incorporation and our by-laws, copies of which are filed with the SEC as exhibits to the registration statement of which this prospectus supplement and the accompanying prospectus are a part.

In this offering, the selling stockholders are offering a maximum of 504,903 shares of common stock.

General

Our authorized capital stock consists of 125,000,000 shares of common stock, \$0.01 par value per share, and 5,000,000 shares of preferred stock, \$0.01 par value per share. As of July 29, 2014, there were 28,595,796 shares of our common stock outstanding and no shares of preferred stock were outstanding.

The following summary description of our capital stock is based on the provisions of our amended and restated certificate of incorporation and amended and restated bylaws and the applicable provisions of the Delaware General Corporation Law. This information is qualified entirely by reference to the applicable provisions of our amended and restated certificate of incorporation, amended and restated bylaws and the Delaware General Corporation Law.

Common Stock

Holders of our common stock are entitled to one vote for each share of common stock held of record for the election of directors and on all matters submitted to a vote of stockholders. Holders of our common stock are entitled to receive dividends ratably, if any, as may be declared by our board of directors out of legally available funds, subject to any preferential dividend rights of any preferred stock then outstanding. Upon our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in our net assets legally available after the payment of all our debts and other liabilities, subject to the preferential rights of any preferred stock then outstanding. Holders of our common stock have no preemptive, subscription, redemption or conversion

S-10

Table of Contents

rights. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. Except as described below in Anti-takeover effects of Delaware law, our certificate of incorporation and our by-laws, a majority vote of common stockholders is generally required to take action under our certificate of incorporation and by-laws.

Preferred Stock

Pursuant to our amended and restated certificate of incorporation, our board of directors has the authority, without further action by the stockholders (unless such stockholder action is required by applicable law or NASDAQ rules), to designate and issue up to 5,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the rights, preferences and privileges of the shares of each wholly unissued series, and any qualifications, limitations or restrictions thereon, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding.

We will fix the rights, preferences and privileges of the preferred stock of each such series, as well as any qualifications, limitations or restrictions thereon, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus supplement and the accompanying prospectus are a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock.

Warrants

As of June 30, 2014, warrants to purchase a total of 337,952 shares of our common stock were outstanding with a weighted average exercise price of \$11.98 per share. These warrants expire beginning in November 2015.

Registration Rights

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

Demand Registration Rights

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

Piggyback Registration Rights

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

S-11

Table of Contents

We will pay all registration expenses, other than underwriting discounts and commissions, related to any demand or piggyback registration. The amended and restated investors' rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders, in the event of misstatements or omissions in the registration statement attributable to us except in the event of fraud and they are obligated to indemnify us for misstatements or omissions attributable to them. The registration rights will terminate upon the later of the date on which all registrable shares have been sold and the fifth anniversary of the closing date of our initial public offering.

Anti-takeover Effects of Delaware Law, our Certificate of Incorporation and our By-Laws

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

Board Composition and Filling Vacancies

In accordance with our certificate of incorporation, our board is divided into three classes serving three-year terms, with one class being elected each year. Our certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of 75% or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office, even if less than a quorum.

No Written Consent of Stockholders

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

Meetings of Stockholders

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

Advance Notice Requirements

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

Amendment to By-Laws and Certificate of Incorporation

As required by the Delaware General Corporation Law, any amendment of our certificate of incorporation must first be approved by a majority of our board of directors and, if required by law or our certificate of incorporation, thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment, and a majority of

S-12

Table of Contents

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

Blank Check Preferred Stock

Our certificate of incorporation provides for 5,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of us or our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Section 203 of the Delaware General Corporation Law

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

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

before the stockholder became interested, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or

at or after the time the stockholder became interested, the business combination was approved by the board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

S-13

Table of Contents

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

Exclusive Jurisdiction of Certain Actions

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

LEGAL MATTERS

The validity of the issuance of the securities offered hereby will be passed upon for us by Goodwin Procter LLP, Boston, Massachusetts.

EXPERTS

The consolidated financial statements of bluebird bio, Inc. as of December 31, 2013 and 2012 and for each of the two years in the period ended December 31, 2013 appearing in the Company's Annual Report (Form 10-K) for the year ended December 31, 2013 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

The consolidated financial statements of bluebird bio, Inc. for the year ended December 31, 2011 incorporated by reference in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2013, have been audited by McGladrey LLP, an independent registered public accounting firm, as stated in their report incorporated by reference herein, and have been so incorporated in reliance upon such report and upon the authority of such firm as experts in accounting and auditing.

Table of Contents

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We have filed with the SEC a registration statement on Form S-3 under the Securities Act of 1933, as amended, or the Securities Act, with respect to the common stock offered by this prospectus supplement. This prospectus supplement, filed as part of the registration statement, does not contain all the information set forth in the registration statement and its exhibits and schedules, portions of which have been omitted as permitted by the rules and regulations of the SEC. For further information about us, we refer you to the registration statement and to its exhibits and schedules.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any materials we file at the SEC's Public Reference Room at 100F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information about the Public Reference Room. The SEC also maintains a website at www.sec.gov that contains periodic and current reports, proxy and information statements, and other information regarding registrants that are filed electronically with the SEC.

These documents are also available, free of charge, through the Investors section of our website, which is located at www.bluebirdbio.com. Information contained on our website is not incorporated by reference into this prospectus supplement or the accompanying prospectus and you should not consider information on our website to be part of this prospectus supplement or the accompanying prospectus.

Table of Contents

PROSPECTUS

bluebird bio, Inc.

Common Stock

Preferred Stock

Warrants

Units

Debt Securities

By this prospectus, we or any selling stockholder may offer and sell from time to time, in one or more offerings, common stock, preferred stock, warrants, debt securities or any combination thereof as described in this prospectus. The warrants may be convertible into or exercisable or exchangeable for common stock or preferred stock, the preferred stock may be convertible into or exchangeable for common stock and the debt securities may be convertible into or exchangeable for common stock or preferred stock. You should carefully read this prospectus, any prospectus supplement and any free writing prospectus, as well as any documents incorporated in any of the foregoing by reference, before you invest in our securities. This prospectus may not be used to sell our securities unless accompanied by a prospectus supplement. The prospectus supplement or any related free writing prospectus may also add to, update, supplement or clarify information contained in this prospectus.

Our common stock is traded on the NASDAQ Global Select Market under the symbol BLUE.

We or any selling stockholder may offer and sell our securities to or through one or more agents, underwriters, dealers or other third parties or directly to one or more purchasers on a continuous or delayed basis. If agents, underwriters or dealers are used to sell our securities, we or any selling stockholder will name them and describe their compensation in a prospectus supplement. The price to the public of our securities and the net proceeds we expect to receive from the sale of such securities will also be set forth in a prospectus supplement. We will not receive any proceeds from the sale of securities by selling stockholders.

INVESTING IN OUR SECURITIES INVOLVES A HIGH DEGREE OF RISK. YOU SHOULD REVIEW CAREFULLY THE RISKS AND UNCERTAINTIES REFERENCED UNDER THE HEADING RISK FACTORS ON PAGE 6 OF THIS PROSPECTUS AS WELL AS THOSE CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND ANY RELATED FREE WRITING PROSPECTUS, AND IN THE OTHER DOCUMENTS THAT ARE INCORPORATED BY REFERENCE INTO THIS PROSPECTUS OR THE APPLICABLE PROSPECTUS SUPPLEMENT.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is July 2, 2014.

Table of Contents

TABLE OF CONTENTS

	Page
<u>ABOUT THIS PROSPECTUS</u>	1
<u>WHERE YOU CAN FIND ADDITIONAL INFORMATION</u>	3
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	4
<u>CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS</u>	5
<u>RISK FACTORS</u>	6
<u>ABOUT THE COMPANY</u>	7
<u>DESCRIPTION OF SECURITIES</u>	8
<u>RATIO OF EARNINGS TO FIXED CHARGES</u>	10
<u>USE OF PROCEEDS</u>	11
<u>SELLING STOCKHOLDERS</u>	12
<u>PLAN OF DISTRIBUTION</u>	13
<u>LEGAL MATTERS</u>	15
<u>EXPERTS</u>	15

We are responsible for the information contained and incorporated by reference in this prospectus, in any accompanying prospectus supplement, and in any related free writing prospectus we prepare or authorize. We have not authorized anyone to give you any other information, and we take no responsibility for any other information that others may give you. If you are in a jurisdiction where offers to sell, or solicitations of offers to purchase, the securities offered by this documentation are unlawful, or if you are a person to whom it is unlawful to direct these types of activities, then the offer presented in this document does not extend to you. The information contained in this document speaks only as of the date of this document, unless the information specifically indicates that another date applies. Our business, financial condition, results of operations and prospectus may have changed since those dates.

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of an automatic shelf registration statement that we filed with the Securities and Exchange Commission, or the SEC, as a well-known seasoned issuer as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration, we and/or selling stockholders may offer shares of our common stock and preferred stock, various series of warrants to purchase common stock or preferred stock, debt securities or any combination thereof, from time to time in one or more offerings. This prospectus only provides you with a general description of the securities we and/or selling stockholders may offer. Each time we and/or selling stockholders offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the specific terms of the offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. This prospectus may not be used to sell our securities unless accompanied by a prospectus supplement. Each such prospectus supplement and any free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in documents incorporated by reference into this prospectus. We urge you to carefully read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the headings **Where You Can Find Additional Information** and **Incorporation of Certain Information by Reference** before you invest in our securities.

Neither we nor any selling stockholder have authorized anyone to provide you with information in addition to or different from that contained in this prospectus, any applicable prospectus supplement and any related free writing prospectus. We take no responsibility for, and can provide no assurances as to the reliability of, any information not contained in this prospectus, any applicable prospectus supplement or any related free writing prospectus that we or a selling stockholder may authorize to be provided to you. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the heading **Where You Can Find Additional Information**.

Unless otherwise mentioned or unless the context requires otherwise, throughout this prospectus, any applicable prospectus supplement and any related free writing prospectus, the words **bluebird bio**, **we**, **us**, **our**, **the company** similar references refer to bluebird bio, Inc. and its subsidiaries; and the term **securities** refers collectively to our common stock, preferred stock, warrants to purchase common stock or preferred stock, debt securities, or any combination of the foregoing securities.

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. This prospectus and the information incorporated herein by reference contains references to trademarks, service marks and trade names owned by us or other companies. Solely for convenience, trademarks, service marks and trade names referred to in this prospectus and the information incorporated herein, 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

Table of Contents

trademarks, service marks and trade names. We do not intend our use or display of other companies' trade names, service marks or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.

Table of Contents

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus is part of a registration statement that we have filed with the SEC. Certain information in the registration statement has been omitted from this prospectus in accordance with the rules of the SEC. We are subject to the information requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and, in accordance therewith, file annual, quarterly and special reports, proxy statements and other information with the SEC. You may read and copy any document we file at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. You may call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room. These documents also may be accessed through the SEC's Electronic Data Gathering, Analysis and Retrieval system, or EDGAR, via electronic means, including the SEC's home page on the Internet (*www.sec.gov*).

We have the authority to designate and issue more than one class or series of stock having various preferences, conversion and other rights, voting powers, restrictions, limitations as to dividends, qualifications, and terms and conditions of redemption. See Description of Securities. We will furnish a full statement of the relative rights and preferences of each class or series of our stock which has been so designated and any restrictions on the ownership or transfer of our stock to any stockholder upon request and without charge. Written requests for such copies should be directed to bluebird bio, Inc., 150 Second Street, Third Floor, Cambridge, Massachusetts 02141, Attention: Secretary, or by telephone request to (339) 499-9300. Our website is located at *http://www.bluebirdbio.com*. Information contained on our website is not incorporated by reference into this prospectus and, therefore, is not part of this prospectus or any accompanying prospectus supplement.

Table of Contents

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference the information and reports we file with it, which means that we can disclose important information to you by referring you to these documents. The information incorporated by reference is an important part of this prospectus, and information that we file after the date hereof with the SEC will automatically update and supersede the information already incorporated by reference. We are incorporating by reference the documents listed below, which we have already filed with the SEC, and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, except as to any portion of any future report or document that is not deemed filed under such provisions, after the date of this prospectus and prior to the termination of this offering:

Annual Report on Form 10-K for the year ended December 31, 2013, as filed with the SEC on March 5, 2014;

The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2013 from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed), which was filed with the SEC on April 24, 2014;

Quarterly Report on Form 10-Q filed with the SEC for the quarter ended March 31, 2014, as filed with the SEC on May 13, 2014;

Current Reports on Form 8-K filed with the SEC on January 13, 2014, February 7, 2014, May 22, 2014, June 11, 2014, June 16, 2014 and June 30, 2014 (in each case, except for information contained therein which is furnished rather than filed); and

The description of our common stock contained in our registration statement on Form 8-A, which was filed with the SEC on June 14, 2013, including any amendment or report filed for the purpose of updating such description.

Upon request, we will provide, without charge, to each person, including any beneficial owner, to whom a copy of this prospectus is delivered a copy of the documents incorporated by reference into this prospectus. You may request a copy of these filings, and any exhibits we have specifically incorporated by reference as an exhibit in this prospectus, at no cost by writing or telephoning us at the following:

bluebird bio, Inc., 150 Second Street, Third Floor, Cambridge, Massachusetts 02141, Attention: Secretary, (339) 499-9300.

You may also access these documents, free of charge on the SEC's website at www.sec.gov or on our website at www.bluebirdbio.com. The information contained in, or that can be accessed through, our website is not part of this prospectus.

This prospectus is part of a registration statement we filed with the SEC. We have incorporated exhibits into this registration statement. You should read the exhibits carefully for provisions that may be important to you.

Neither we nor any selling stockholder have authorized anyone to provide you with information other than what is incorporated by reference or provided in this prospectus or any prospectus supplement. Neither we nor any selling stockholder are making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus or in the documents incorporated by reference is accurate as of any date other than the date on the front of this prospectus or those documents.

Table of Contents

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the documents that we incorporate by reference, contains forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. These statements are often, but are not always, made through the use of words or phrases such as may, will, could, should, expects, intends, plans, anticipates, believes, estimates, predicts, continue, and similar expressions, or the negative of these terms, or similar expressions. Accordingly, these statements involve estimates, assumptions and uncertainties which could cause actual results to differ materially from those expressed in them. Any forward-looking statements are qualified in their entirety by reference to the factors discussed throughout this report, and in particular those factors referenced in the section Risk Factors.

This prospectus, including the sections entitled About this Prospectus and Risk Factors, contains forward-looking statements that are based on our management's belief and assumptions and on information currently available to our management. These statements relate to future events or our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. 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.

Given these uncertainties, you should not place undue reliance on these forward-looking statements. You should read this prospectus, any supplements to this prospectus and the documents that we incorporate by reference in this prospectus with the understanding that our actual future results may be materially different from what we expect. Except as required by law, we do not undertake any obligation to update or revise any forward-looking statements contained in this prospectus or any supplement to this prospectus, whether as a result of new information, future events or otherwise.

Table of Contents

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider the risks described in the documents incorporated by reference in this prospectus and any prospectus supplement, as well as other information we include or incorporate by reference into this prospectus and any applicable prospectus supplement, before making an investment decision. Our business, financial condition or results of operations could be materially adversely affected by the materialization of any of these risks. The trading price of our securities could decline due to the materialization of any of these risks, and you may lose all or part of your investment. This prospectus and the documents incorporated herein by reference also contain forward-looking statements that involve risks and uncertainties. Actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks described in the documents incorporated herein by reference, including (i) our most recent annual report on Form 10-K which is on file with the SEC and is incorporated herein by reference, (ii) our most recent quarterly report on Form 10-Q, which is on file with the SEC and is incorporated by reference into this prospectus, and (iii) other documents we file with the SEC that are deemed incorporated by reference into this prospectus.

Table of Contents

ABOUT THE COMPANY

We are a clinical-stage biotechnology company focused on transforming the lives of patients with severe genetic and orphan diseases using gene therapy.

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

We also are conducting Phase I/II clinical studies in both the United States and Europe of our next most advanced product candidate, LentiGlobin, to evaluate its safety and efficacy in subjects with β -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 December 2013, we announced that the first subject with β -thalassemia major had been treated in our European study. In March 2014, we announced that the first subject with β -thalassemia major had been treated in our study in the United States. We presented initial results from the European clinical study of β -thalassemia major at the European Hematology Association Congress in Milan, Italy in June 2014.

We also have an active investigational new drug application in the United States for a Phase I/II clinical study to evaluate the safety and efficacy of LentiGlobin in subjects with severe SCD. We are planning to treat the first SCD patient with our LentiGlobin product candidate in 2014. Orphan drug status has been granted for LentiGlobin for the treatment of SCD by U.S. regulatory authorities.

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

We were incorporated in Delaware in April 1992 under the name Genetix Pharmaceuticals, Inc., and subsequently changed our name to bluebird bio, Inc. in September 2010. Our mailing address and executive offices are located at 150 Second Street, Third Floor, Cambridge, Massachusetts and our telephone number at that address is (339) 499-9300. We maintain an Internet website at the following address: www.bluebirdbio.com. The information on, or that can be accessed through, our website does not constitute part of this prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock. Our common stock trades on the NASDAQ Global Select Market under the symbol BLUE.

Table of Contents

DESCRIPTION OF SECURITIES

We and/or any selling stockholder may offer shares of our common stock and preferred stock, various series of warrants to purchase common stock or preferred stock, debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt, or any combination thereof from time to time in one or more offerings under this prospectus at prices and on terms to be determined at the time of any offering. This prospectus provides you with a general description of the securities we and/or any selling stockholder may offer. Each time we and/or any selling stockholder offer a type or series of securities under this prospectus, we will provide a prospectus supplement and/or free writing prospectus that will describe the specific amounts, prices and other important terms of the securities.

Common Stock. We and/or any selling stockholder may issue and/or sell, as applicable, shares of our common stock from time to time. Holders of shares of our common stock are entitled to one vote for each share held of record on all matters to be voted on by stockholders and do not have cumulative voting rights. Subject to the preferences that may be applicable to any then outstanding preferred stock, the holders of our outstanding shares of common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds. In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities, subject to the satisfaction of any liquidation preference granted to the holders of any outstanding shares of preferred stock.

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the rights, preferences and privileges of the shares of each wholly unissued series, and any qualifications, limitations or restrictions thereon, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the rights, preferences and privileges of the preferred stock of such series, as well as any qualifications, limitations or restrictions thereon, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Warrants. We may issue warrants for the purchase of common stock and/or preferred stock in one or more series. We may issue warrants independently or together with common stock and/or preferred stock, and the warrants may be attached to or separate from these securities. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the particular series of warrants being offered, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants. Forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

We will evidence each series of warrants by warrant certificates that we will issue. Warrants may be issued under an applicable warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if applicable, in the prospectus supplement relating to the particular series of warrants being offered.

Table of Contents

Units. We may issue, in one or more series, units consisting of common stock, preferred stock, and/or warrants for the purchase of common stock and/or preferred stock in any combination. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreement that contains the terms of the units. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of unit agreement and any supplemental agreements that describe the terms of the series of units we are offering before the issuance of the related series of units.

We will evidence each series of units by unit certificates that we will issue. Units may be issued under a unit agreement that we enter into with a unit agent. We will indicate the name and address of the unit agent, if applicable, in the prospectus supplement relating to the particular series of units being offered.

Debt Securities. We may issue debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. In this prospectus, we have summarized certain general features of the debt securities. We urge you, however, to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the particular series of debt securities being offered, as well as the complete indenture that contains the terms of the debt securities. We will file as exhibits to the registration statement of which this prospectus is a part, the form of indenture and any supplemental agreements that describe the terms of the series of debt securities we are offering before the issuance of the related series of debt securities.

We may evidence each series of debt securities we will issue by an indenture that we enter into with a trustee. We will indicate the name and address of the trustee, if applicable, in the prospectus supplement relating to the particular series of debt securities being offered.

Table of Contents

RATIO OF EARNINGS TO FIXED CHARGES

Our ratio of earnings to fixed charges for recently completed fiscal years and any required interim periods will be specified in a prospectus supplement or in a document that we file with the SEC and incorporate by reference in the future.

Table of Contents

USE OF PROCEEDS

Except as described in any prospectus supplement or in any related free writing prospectus that we may authorize to be provided to you, the net proceeds received by us from our sale of the securities described in this prospectus will be added to our general funds and will be used for our general corporate purposes. From time to time, we may engage in additional public or private financings of a character and amount which we may deem appropriate. Unless otherwise set forth in a prospectus supplement, we will not receive any proceeds from the sale of securities by any selling stockholder.

Table of Contents

SELLING STOCKHOLDERS

Selling stockholders are persons or entities that, directly or indirectly, have acquired or will from time to time acquire from us, our securities. Such selling stockholders may be parties to registration rights agreements with us, or we otherwise may have agreed or will agree to register their securities for resale. The initial purchasers of our securities, as well as their transferees, pledges, donees or successors, all of whom we refer to as selling stockholders, may from time to time offer and sell our securities pursuant to this prospectus and any applicable prospectus supplement.

The applicable prospectus supplement will set forth the name of each of the selling stockholders and the number of securities beneficially owned by such selling stockholder that are covered by such prospectus supplement. The applicable prospectus supplement will also disclose whether any of the selling stockholders has held any position or office with, has been employed by or otherwise has had a material relationship with us during the three years prior to the date of the applicable prospectus supplement.

Table of Contents

PLAN OF DISTRIBUTION

We and/or any selling stockholder may sell our securities from time to time in one or more transactions. We and/or any selling stockholder may sell our securities to or through agents, underwriters, dealers, remarketing firms or other third parties or directly to one or more purchasers or through a combination of any of these methods. In some cases, we and/or any selling stockholder or dealers acting with us and/or any selling stockholder or on behalf of us and/or any selling stockholder may also purchase our securities and reoffer them to the public. We and/or any selling stockholder may also offer and sell, or agree to deliver, our securities pursuant to, or in connection with, any option agreement or other contractual arrangement.

Agents whom we designate may solicit offers to purchase our securities.

We and/or any selling stockholder will name any agent involved in offering or selling our securities, and disclose any commissions that we will pay to the agent, in the applicable prospectus supplement.

Unless we and/or any selling stockholder indicate otherwise in the applicable prospectus supplement, agents will act on a best efforts basis for the period of their appointment.

Agents may be deemed to be underwriters under the Securities Act, of any of our securities that they offer or sell.

We and/or any selling stockholder may use an underwriter or underwriters in the offer or sale of our securities.

If we and/or any selling stockholder use an underwriter or underwriters, we will execute an underwriting agreement with the underwriter or underwriters at the time that we reach an agreement for the sale of our securities.

We and/or any selling stockholder will include the names of the specific managing underwriter or underwriters, as well as the names of any other underwriters, and the terms of the transactions, including the compensation the underwriters and dealers will receive, in the applicable prospectus supplement.

The underwriters will use the applicable prospectus supplement, together with the prospectus, to sell our securities.

We may use a dealer to sell our securities.

If we and/or any selling stockholder use a dealer, we will sell our securities to the dealer, as principal.

The dealer will then sell our securities to the public at varying prices that the dealer will determine at the time it sells our securities.

We and/or any selling stockholder will include the name of the dealer and the terms of the transactions with the dealer in the applicable prospectus supplement.

We and/or any selling stockholder may solicit directly offers to purchase our securities, and we may directly sell our securities to institutional or other investors. We and/or any selling stockholder will describe the terms of direct sales in the applicable prospectus supplement.

We and/or any selling stockholder may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) of the Securities Act.

We and/or any selling stockholder will indemnify agents, underwriters and dealers against certain liabilities, including liabilities under the Securities Act. Agents, underwriters and dealers, or their affiliates, may be customers of, engage in transactions with or perform services for us or our respective affiliates, in the ordinary course of business.

Table of Contents

We and/or any selling stockholder may authorize agents and underwriters to solicit offers by certain institutions to purchase our securities at the public offering price under delayed delivery contracts.

If we and/or any selling stockholder use delayed delivery contracts, we will disclose that we are using them in the prospectus supplement and will tell you when we will demand payment and when delivery of our securities will be made under the delayed delivery contracts.

These delayed delivery contracts will be subject only to the conditions that we describe in the prospectus supplement.

We and/or any selling stockholder will describe in the applicable prospectus supplement the commission that underwriters and agents soliciting purchases of our securities under delayed delivery contracts will be entitled to receive.

Unless otherwise specified in connection with a particular underwritten offering of our securities, the underwriters will not be obligated to purchase offered securities unless specified conditions are satisfied, and if the underwriters do purchase any offered securities, they will purchase all offered securities.

In connection with underwritten offerings of the offered securities and in accordance with applicable law and industry practice, the underwriters in certain circumstances are permitted to engage in certain transactions that stabilize the price of our securities. Such transactions consist of bids or purchases for the purpose of pegging, fixing or maintaining the price of our securities. If the underwriters create a short position in our securities in connection with the offering (*i.e.*, if they sell more securities than are set forth on the cover page of the applicable prospectus supplement), the underwriters may reduce that short position by purchasing our securities in the open market or as otherwise provided in the applicable prospectus supplement. The underwriters may also impose a penalty bid, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if the securities sold by them are repurchased in connection with stabilization transactions. In general, purchases of a security for the purpose of stabilization or to reduce a short position could cause the price of the security to be higher than it might be in the absence of such purchases. The imposition of a penalty bid might also have an effect on the price of our securities to the extent that it were to discourage resales of our securities. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and/or any selling stockholder may effect sales of securities in connection with forward sale, option or other types of agreements with third parties. Any distribution of securities pursuant to any forward sale agreement may be effected from time to time in one or more transactions that may take place through a stock exchange, including block trades or ordinary broker's transactions, or through broker-dealers acting either as principal or agent, or through privately-negotiated transactions, or through an underwritten public offering, or through a combination of any such methods of sale, at market prices prevailing at the time of sale, prices relating to such prevailing market prices or at negotiated or fixed prices.

The specific terms of the lock-up provisions, if any, in respect of any given offering will be described in the applicable prospectus supplement.

In compliance with the guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8.0% of

the aggregate amount of the securities offered by this prospectus.

Table of Contents

LEGAL MATTERS

The validity of the securities being offered by this prospectus will be passed upon by Goodwin Procter LLP, Boston, Massachusetts.

EXPERTS

The consolidated financial statements of bluebird bio, Inc. as of December 31, 2013 and 2012 and for each of the two years in the period ended December 31, 2013 appearing in the Company's Annual Report (Form 10-K) for the year ended December 31, 2013 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

The consolidated financial statements of bluebird bio, Inc. for the year ended December 31, 2011 incorporated by reference in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2013, have been audited by McGladrey LLP, an independent registered public accounting firm, as stated in their report incorporated by reference herein, and have been so incorporated in reliance upon such report and upon the authority of such firm as experts in accounting and auditing.

Table of Contents

PROSPECTUS SUPPLEMENT

July 30, 2014