Filed Pursuant to 424(b)(5)
Registration No. 333-236489

Prospectus Supplement
(To Prospectus dated February 18, 2020)

Up to $75,000,000

Common Stock

We, bluebird bio, Inc., have entered into an equity distribution agreement with Goldman Sachs & Co. LLC, as our sales agent, relating to common stock, par value $0.01 per share, offered by this prospectus supplement. In accordance with the terms of the equity distribution agreement, we may offer and sell common stock having an aggregate offering price of up to $75.0 million from time to time through or to the sales agent, acting as our agent or principal.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "BLUE". The last reported sale price of our common stock on June 21, 2022 was $4.16 per share.

Sales of our common stock, if any, under this prospectus supplement and the accompanying prospectus will be made in sales deemed to be "at the market offerings" as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act, in ordinary brokers' transactions, to or through a market maker, on or through the Nasdaq Global Select Market or any other market venue where the securities may be traded, in the over-the-counter market, in privately negotiated transactions, or through a combination of any such methods of sale. The sales agent may also sell our common stock by any other method permitted by law. The sales agent is not required to sell any specific amount of securities but, subject to the terms and conditions of the equity distribution agreement, has agreed to use its reasonable efforts consistent with its normal trading and sales practices to sell shares of our common stock up to the amount specified. There is no arrangement for funds to be received in any escrow, trust, or similar arrangement.

Under the equity distribution agreement, we may also sell common stock to the sales agent as principal for their own accounts, at a price to be agreed upon at the time of sale. If we sell common stock to the sales agent as principal, we will enter into a separate terms agreement with the sales agent, and we will describe the agreement in a separate prospectus supplement or pricing supplement.

The compensation to the sales agent for sales of common stock sold pursuant to the equity distribution agreement will be up to 3% of the gross proceeds of any common stock sold under the equity distribution agreement. In connection with the sale of the common stock on our behalf, the sales agent will be deemed to be an "underwriter" within the meaning of the Securities Act, and the compensation of the sales agent will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to the sales agent with respect to certain liabilities, including liabilities under the Securities Act or the Securities Exchange Act of 1934, as amended, or the Exchange Act.

Investing in our common stock involves a high degree of risk. See "Risk Factors" on page S-5 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement before investing in our common stock.

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

Goldman Sachs & Co. LLC

June 22, 2022

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Prospectus Supplement

Prospectus

We have not, and the sales agent has not, authorized anyone to provide you with different information than that contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering. We are not, and the sales agent is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus supplement entitled “Where You Can Find Additional Information” and “Incorporation of Certain Information by Reference.”

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated February 18, 2020, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date-for example, a document incorporated by reference in this prospectus supplement-the statement in the document having the later date modifies or supersedes the earlier statement. You should assume that the information contained in this prospectus supplement is accurate as of the date on the cover page of this prospectus supplement only and that any information we have incorporated by reference or included in the accompanying prospectus is accurate only as of the date given in the document incorporated by reference or as of the date of the prospectus, as applicable, regardless of the time of delivery of this prospectus supplement or the accompanying prospectus or any sale of our common stock. Our business, financial condition, results of operations, and prospects may have changed since that date.

Unless otherwise mentioned or unless the context requires otherwise, all references in this prospectus supplement to “bluebird,” “the Company,” “we,” “us,” “our,” or similar references mean bluebird bio, Inc. and our subsidiaries, on a consolidated basis.

This prospectus supplement contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus supplement, including logos, artwork, and other visual displays, may appear without the ® or TM symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. 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.

The industry and market data and other statistical information contained in this prospectus supplement, the accompanying prospectus, and the documents we incorporate by reference are based on management’s own estimates, independent publications, government publications, reports by market research firms, or other published independent sources, and, in each case, are believed by management to be reasonable estimates. Although we believe these sources are reliable, we have not independently verified the information.

PROSPECTUS SUPPLEMENT SUMMARY

The following summary highlights and, in certain cases, updates some of the information contained elsewhere in this prospectus supplement and the accompanying prospectus and the documents incorporated by reference. Because this is only a summary, however, it does not contain all of the information that may be important to you. You should carefully read this entire prospectus supplement and the accompanying prospectus, and the information incorporated by reference herein, especially the matters discussed under "Risk Factors" beginning on page S-5 of this prospectus supplement and the "Risk Factors" sections of our Annual Report on Form 10-K for the year ended December 31, 2021 and our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2022, along with our consolidated financial statements and notes thereto, before making an investment decision.

Company Overview

In 2021, we completed the tax-free spin-off of our oncology programs and portfolio to become a company focused on the pursuit of curative gene therapies for severe genetic diseases. Today, bluebird bio, Inc. has industry-leading, late-stage clinical programs for the treatment of sickle cell disease, b-thalassemia and cerebral adrenoleukodystrophy. Using a proprietary lentiviral vector ("LVV") platform, we custom design each of our therapies to address the underlying cause of disease by introducing a functional copy of a gene to patients' own isolated hematopoietic stem cells. In a rapidly advancing field, we have developed in-depth analytical methods to understand the safety of our LVV technologies, which are designed to deliver a sustained, lifelong response from a one-time treatment and to improve upon allogeneic hematopoietic stem cell transplant ("HSCT"), which carries significant limitations, including the ability to identify matched donors, risk of transplant-related graft-vs-host disease and death, as well as to improve upon current treatment approaches used with patients not currently eligible to receive allogeneic HSCT. We have the largest and deepest ex vivo gene therapy data set in the industry, with more than 500 patient years of experience. Long-term, we seek to build our pipeline by investing in in vivo applications of our LVV platform in sickle cell disease.

Corporate Information

We were incorporated in Delaware in April 1992 under the name Genetix Pharmaceuticals, Inc., and subsequently changed our name to bluebird bio, Inc. in September 2010.

Our mailing address and executive offices are located at 455 Grand Union Boulevard, Somerville, 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.

Recent Developments

In April 2022, we provided our expectations for anticipated cost savings from a comprehensive restructuring initiative. We are updating those anticipated cost savings and expect that the restructuring initiative will reduce the Company's cash burn in 2022 to approximately $345 million, reflecting up to approximately $55 million in aggregate cost savings for the calendar year. Our expectations regarding the continuation of these cost savings into 2023 will be further refined in our 2023 operational budget and will be affected by many factors, including the outcome of the Prescription Drug User Fee Act goal date for each of beti-cel and eli-cel. These expectations are based on estimates and the judgment of management. We may not realize the expected cost savings from the restructuring at the levels we expect, and they could be substantially lower than we expect, and our cash runway may not extend as far as we have forecast. See "Risk Factors—If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements are incorrect, our actual results may vary from those reflected in our projections and accruals."

THE OFFERING

Common stock offered by us	Shares of our common stock having an aggregate offering price of up to $75.0 million.
Common stock to be outstanding immediately after this offering	Up to 89,467,339 shares of our common stock (as more fully described in the notes following this table), assuming sales of 18,028,846 shares of common stock in this offering at an offering price of $4.16 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on June 21, 2022. The actual number of shares of common stock issued will vary depending on the sale price under this offering.
Manner of offering	"At the market offering" that may be made from time to time through or to Goldman Sachs & Co. LLC, as our sales agent or principal. See "Plan of Distribution" for more information.
Use of proceeds	We currently intend to use the net proceeds from this offering, together with our existing cash: • to complete ongoing clinical trials of our product candidates and to seek the regulatory approval of our product candidates; • to finance the commercial launch and manufacturing of our product candidates, if approved; and • for other general corporate and working capital purposes. See "Use of Proceeds" for more information.
Risk factors	Investing in our common stock involves a high degree of risk. See "Risk Factors" for more information.
Nasdaq Global Select Market symbol	"BLUE"

The number of shares of common stock to be outstanding after this offering is based on 71,438,493 shares of common stock outstanding as of March 31, 2022, and excludes:

- 5,645,025 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2022, at a weighted average exercise price of $36.52 per share;
- 4,052,526 shares of common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2022;
- 2,272,727 shares of common stock issuable upon the exercise of warrants outstanding as of March 31, 2022;
- 4,502,368 shares of common stock reserved for future issuance under our 2013 Stock Option and Incentive Plan, or the 2013 Plan, as of March 31, 2022, plus any future increases in the number of shares of common stock reserved for issuance under the 2013 Plan pursuant to the evergreen provision of the 2013 Plan;

- 1,346,964 shares of common stock reserved for future issuance under our 2013 Employee Stock Purchase Plan, or ESPP, as of March 31, 2022; and
- 828,383 shares of common stock reserved for future issuance under our 2021 Inducement Plan, or Inducement Plan, as of March 31, 2022.

Unless otherwise indicated, all information contained in this prospectus supplement assumes no exercise of the outstanding options and restricted stock units described above.

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before you invest in our common stock, you should carefully consider the risks described below, as well as general economic and business risks and the other information in this prospectus supplement and in the documents incorporated by reference herein, including those set forth under the heading "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2021 and under the heading "Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2022. The occurrence of any of the events or circumstances described below or other adverse events could have a material adverse effect on our business, results of operations and financial condition and could cause the trading price of our common stock to decline. Additional risks or uncertainties not presently known to us or that we currently deem immaterial may also harm our business. Any of the following risks as well as the risks discussed in the documents incorporated by reference herein, could have a material adverse effect on our business, operating results and financial condition and cause the trading price of our common stock to decline, which would cause you to lose all or part of your investment. When determining whether to invest, you should also refer to the other information contained or incorporated by reference in this prospectus supplement, including our financial statements and the related notes thereto. The risks and uncertainties described below are not the only ones we face.

Risks Related to This Offering

If you purchase shares of our common stock sold in this offering, you will experience immediate and substantial dilution in the net tangible book value of your shares. In addition, we may issue additional equity or convertible debt securities in the future, which may result in additional dilution to you.

The price per share of our common stock being offered may be higher than the net tangible book value per share of our outstanding common stock prior to this offering. Assuming that an aggregate of 18,028,846 shares of our common stock are sold at a price of $4.16 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on June 21, 2022, for aggregate gross proceeds of approximately $75.0 million, and after deducting commissions and estimated offering expenses payable by us, new investors in this offering will incur immediate dilution of $0.47 per share, representing the difference between our as adjusted net tangible book value per share as of March 31, 2022 of approximately $3.69, after giving effect to this offering, and the assumed offering price. For a more detailed discussion of the foregoing, see the section entitled "Dilution" below. To the extent outstanding stock options are exercised or outstanding restricted stock units vest, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future and we issue additional shares of common stock or securities convertible or exchangeable for our common stock, our then existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

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

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled "Use of Proceeds," and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply our net proceeds in ways that ultimately increase the value of your investment. We expect to use the net proceeds from this offering to complete ongoing clinical trials of our product candidates and to seek the regulatory approval of our product candidates, to finance the commercial launch and manufacturing of our product candidates, if approved and for other general corporate and working capital purposes. The failure by our management to apply these funds effectively could harm our business. Pending their use, we plan to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government. These investments may not yield a favorable return to our stockholders. If we do not invest or apply the net proceeds from this

offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

Future sales or issuances of our common stock in the public markets, or the perception of such sales, could depress the trading price of our common stock.

The sale of a substantial number of shares of our common stock or other equity-related securities in the public markets, or the perception that such sales could occur, could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities. We may sell large quantities of our common stock at any time pursuant to this prospectus supplement or in one or more separate offerings. We cannot predict the effect that future sales of common stock or other equity-related securities would have on the market price of our common stock.

The actual number of shares we will issue under the equity distribution agreement, at any one time or in total, is uncertain.

Subject to certain limitations in the equity distribution agreement and compliance with applicable law, we have the discretion to deliver a placement notice to Goldman Sachs & Co. LLC at any time throughout the term of the equity distribution agreement. The number of shares that are sold by Goldman Sachs & Co. LLC after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with Goldman Sachs & Co. LLC. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued.

The common stock offered hereby will be sold in "at the market offerings," and investors who buy shares at different times will likely pay different prices.

Investors who purchase shares in this offering at different times will likely pay different prices, and so may experience different outcomes in their investment results. We will have discretion, subject to market demand, to vary the timing, prices, and numbers of shares sold, and there is no minimum or maximum sales price. Investors may experience a decline in the value of their shares as a result of share sales made at prices lower than the prices they paid.

If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements are incorrect, our actual results may vary from those reflected in our projections and accruals.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP"). The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct. We may be incorrect in our assumptions regarding the applicability of drug pricing programs and rebates that may be applicable to our potential products, which may result in our under- or over estimating our anticipated product revenues especially as applicable laws and regulations governing pricing evolve over time. In addition, to the extent payment for our potential products is subject to outcomes-based arrangements over time, the total payments received from product sales may vary, our cash collection of future payments and revenue assumptions from product sales will be at risk, and the timing of revenue recognition may not correspond to the timing of cash collection.

Further, from time to time we issue financial guidance relating to our expectations for certain financial measures, including our cash, cash equivalents, and marketable securities available for operations and expected cost savings from initiatives, which guidance is based on estimates and the judgment of management. For

instance, we previously provided our expectations for our anticipated cost savings from the comprehensive restructuring we announced in April 2022. We are updating those anticipated cost savings and expect that the restructuring initiative will reduce the Company's cash burn in 2022 to approximately $345 million, reflecting up to approximately $55 million in aggregate cost savings for the calendar year. Our expectations regarding the continuation of these cost savings into 2023 will be further refined in our 2023 operational budget and will be affected by many factors. We may not realize the expected cost savings from the restructuring at the levels we expect, and they could be substantially lower than we expect, and our cash runway may not extend as far as we have forecast. Factors that may impact our financial expectations from our previously announced restructuring include, among others, the outcome of the Prescription Drug User Fee Act goal date for beti-cel and eli-cel, respectively, our ability to reduce external expenses and headcount on our anticipated timing, the release of restricted cash related to our 50 Binney Street sublease, the reduction of capital expenses based upon our anticipated changes to our laboratory, research, and clinical strategy, potential funding from future equity issuances, and the potential sale of priority review vouchers. If, for any reason, our expenses differ materially from our guidance or we utilize our cash more quickly than anticipated, we may have to adjust our publicly announced financial guidance. If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline.

Insertional oncogenesis is a risk of gene therapies using viral vectors that can integrate into the genome, and several patients with CALD treated with eli-cel in our clinical studies have been diagnosed with MDS likely mediated by Lenti-D LVV insertion. These events may require us to halt or delay further clinical development of our product candidates, such as eli-cel, or to suspend or cease commercialization following marketing approval, and the commercial potential of our product candidates may be materially and negatively impacted.

A potentially significant risk in any gene therapy product using viral vectors that can integrate into the genome is that the vector will insert in or near cancer-causing genes, leading to the proliferation of certain cellular clones that can cause cancer in the patient, known as insertional oncogenesis. Several patients with CALD treated with elicel in our clinical studies have been diagnosed with MDS likely mediated by Lenti-D LVV insertion, and as a result, the FDA placed our clinical studies of eli-cel on clinical hold. In light of the FDA's requests for additional information about safety events and monitoring in the eli-cel clinical program, we have no assurances as to whether we will successfully resolve the clinical hold. In addition, we cannot make assurances that additional patients treated with eli-cel, beti-cel or lovo-cel in the clinical or commercial setting will not be diagnosed with MDS, leukemia or lymphoma. Patients treated with our therapies, including lovo-cel, have exhibited persistent oligoclonality, in which a portion of their hematopoietic system is comprised of cells containing at least one insertion site, as measured by integration site analysis. Based on our pharmacovigilance protocols, we increase our monitoring of patients who exhibit persistent oligoclonality. It is not clear at this time whether persistent oligoclonality represents an increased risk of developing MDS, leukemia, or lymphoma in the future, but it is a criteria used by the FDA to evaluate the safety of gene therapies over time.There is also the potential risk of other 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 LVV 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, we may not receive marketing approval for our product candidates, and we may be unable to commercialize any approved product. It is possible that upon occurrence or recurrence of any of these events, the FDA may place one or more of our programs on hold, impose requirements that result in delays for regulatory approval for one or more of our programs, require risk evaluation or mitigation strategies as a condition for regulatory approval, or may cause us to cease commercialization following the receipt of any marketing approval. If any of these were to occur, the commercial potential of our programs may be materially and negatively impacted.

Furthermore, treatment with our potential products involve chemotherapy or myeloablative treatments which can cause side effects or adverse events that may impact the perception of the potential benefits of our potential products. For instance, MDS leading to acute myeloid leukemia is a known risk of certain myeloablative regimens. Additionally, beti-cel, eli-cel, or lovo-cel, the procedures associated with their

administration, or with the collection of patients' cells, could potentially cause other adverse events that have not yet been predicted. The inclusion of patients with significant underlying medical problems 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, or the progression of their disease. For instance, it is possible that the events of MDS and acute myeloid leukemia (AML) previously reported in our HGB-206 clinical study were caused by lovo-cel, in combination with underlying SCD, transplant procedure, conditioning, and stress on the bone marrow following drug product infusion. Two patients originally in HGB-206 Group A developed acute myeloid leukemia during the long-term follow-up of the study. The two patients ultimately died from complications of AML. Even if a product such as lovo-cel, eli-cel or beti-cel is ultimately approved, such safety events may result in the product being removed from the market or its market opportunity being significantly reduced. Other patients receiving our product candidates may develop leukemia, lymphoma, or MDS in the future, which may negatively impact the commercial prospects of our product candidates. Any of these events could impair our ability to develop or commercialize our product candidates, and their commercial potential may be materially and negatively impacted.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

- the initiation, timing, progress and results of our clinical studies, and our research and development programs;
- our ability to successfully complete clinical studies;
- our ability to obtain adequate financing to fund our operations and to execute on our strategy;
- our ability to establish and scale commercial viral vector and drug product manufacturing capabilities, and to ensure adequate supply of our viral vectors and drug products;
- the timing or likelihood of regulatory filings and marketing approvals for our product candidates;
- the timing or success of commercialization of any approved products;
- our ability to obtain adequate pricing and reimbursement of any approved products;
- 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, cost savings, cash burn, future revenues, capital requirements and our needs for additional financing;
- our ability to maintain and establish collaborations and licenses;
- developments relating to our competitors and our industry;
- the impact of the COVID-19 pandemic;
- the effects, costs, and benefits of the separation of our portfolio of products and programs into two independent, publicly-traded companies;
- other risks and uncertainties, including those listed under "Risk Factors" beginning on page S-5 of this prospectus supplement; and
- our intended use of proceeds from this offering.

Any forward-looking statements in this prospectus supplement, the accompanying prospectus or the documents incorporated by reference reflect our views as of the date on which they are made with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under "Risk Factors" beginning on page S-5 of this prospectus supplement, in "Item 1A. Risk Factors" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2021, in "Item 1A. Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2022 and elsewhere in this

prospectus supplement, the accompanying prospectus and documents incorporated by reference. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

You should read this prospectus supplement, the accompanying prospectus and the documents that we reference in this prospectus supplement and have filed with the SEC as exhibits to the registration statement of which this prospectus supplement is a part and documents incorporated by reference herein with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect.

USE OF PROCEEDS

We may issue and sell shares of common stock having aggregate sales proceeds of up to $75.0 million from time to time. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions, and proceeds to us, if any, are not determinable at this time. There can be no assurance that we will sell any shares of our common stock under or fully utilize the equity distribution agreement with the sales agent as a source of financing.

We currently plan to use the net proceeds we receive from this offering, together with our existing cash:

- to complete ongoing clinical trials of our product candidates and to seek the regulatory approval of our product candidates;
- to finance the commercial launch and manufacturing of our product candidates, if approved; and
- for other general corporate and working capital purposes.

Our expected use of net proceeds from this offering represents our current intentions based upon our present plans and business condition. As of the date of this prospectus supplement, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering or the amounts that we will actually spend on the uses set forth above. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary gene therapy businesses, technologies, products or assets.

The amount and timing of our actual expenditures will depend upon numerous factors, including the timing and success of our ongoing clinical studies and the timing of regulatory submissions and potential approvals. As a result, our management will have broad discretion over the use of the net proceeds from this offering.

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

DILUTION

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

Our historical net tangible book value as of March 31, 2022 was approximately $257.6 million, or approximately $3.61 per share. Our historical net tangible book value is the amount of our total tangible assets less our total liabilities. Historical net tangible book value per share represents historical net tangible book value divided by the 71,438,493 shares of common stock outstanding as of March 31, 2022.

After giving effect to the sale of $75.0 million of shares of our common stock in this offering assuming for illustrative purposes that an aggregate of 18,028,846 shares of our common stock are sold during the term of the equity distribution agreement at a price of $4.16 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on June 21, 2022, and after deducting estimated offering commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2022, would have been approximately approximately $330.1 million, or approximately $3.69 per share. This represents an immediate increase in net tangible book value of $0.08 per share to existing stockholders and immediate dilution in net tangible book value of $0.47 per share to investors purchasing shares of our common stock in this offering at the assumed public offering price.

The following table illustrates this dilution on a per-share basis:

Public offering price per share		$4.16
Historical net tangible book value per share as of March 31, 2022	$3.61	
Increase in as adjusted net tangible book value per share attributable to this offering	0.08	
As adjusted net tangible book value per share after this offering		3.69
Dilution per share to new investors purchasing common stock in this offering		$0.47

The above table is based on 71,438,493 shares of common stock outstanding as of March 31, 2022, and excludes as of that date:

- 5,645,025 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2022, at a weighted average exercise price of $36.52 per share;
- 4,052,526 shares of common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2022;
- 2,272,727 shares of common stock issuable upon the exercise of warrants outstanding as of March 31, 2022;
- 4,502,368 shares of common stock reserved for future issuance under the 2013 Plan as of March 31, 2022;
- 1,346,964 shares of common stock reserved for future issuance under our ESPP as of March 31, 2022; and
- 828,383 shares of common stock reserved for future issuance under our Inducement Plan as of March 31, 2022.

To the extent that any options are exercised, new options are issued under our equity incentive plans, or we otherwise issue additional shares of common stock in the future (including shares issued in connection with acquisitions), there will be further dilution to new investors.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following discussion is a summary of the material U.S. federal income tax consequences to Non-U.S. Holders (as defined below) of the purchase, ownership and disposition of our common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or non-U.S. tax laws are not discussed. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service, or the IRS, in each case in effect as of the date hereof. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a Non-U.S. Holder. We have not sought and will not seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position to the discussion below regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to Non-U.S. Holders that hold our common stock as a "capital asset" within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a Non-U.S. Holder's particular circumstances, including the impact of the Medicare contribution tax on net investment income and the alternative minimum tax. In addition, it does not address consequences relevant to Non-U.S. Holders subject to special rules, including, without limitation:

- U.S. expatriates and former citizens or long-term residents of the United States;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies and other financial institutions;
- real estate investment trusts or regulated investment companies;
- brokers, dealers or traders in securities or currencies;
- "controlled foreign corporations," "passive foreign investment companies" and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- "qualified foreign pension funds" as defined in Section 897(l)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds;
- persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and
- tax-qualified retirement plans.

If an entity treated as a partnership for U.S. federal income tax purposes holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level. Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS FOR INFORMATIONAL PURPOSES ONLY AND IS NOT TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR

SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of a Non-U.S. Holder

For purposes of this discussion, a "Non-U.S. Holder" is any beneficial owner of our common stock that is neither a "U.S. person" nor an entity treated as a partnership for U.S. federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is or is treated as any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust that (1) is subject to the primary supervision of a U.S. court and the control of one or more "United States persons" (within the meaning of Section 7701(a)(30) of the Code), or (2) has a valid election in effect to be treated as a United States person for U.S. federal income tax purposes.

Distributions

We have not paid any cash dividends on our common stock since inception and do not anticipate paying cash dividends in the foreseeable future. However, if we do make distributions of cash or property on our common stock, such distributions will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a Non-U.S. Holder's adjusted tax basis in its common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below under "— Sale or Other Taxable Disposition."

Subject to the discussion below regarding effectively connected income, dividends paid to a Non-U.S. Holder will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty, provided the Non-U.S. Holder furnishes a valid IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) certifying qualification for the lower treaty rate). A Non-U.S. Holder that does not timely furnish the required documentation, but that qualifies for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS. Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under any applicable tax treaties.

If dividends paid to a Non-U.S. Holder are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such dividends are attributable), the Non-U.S. Holder will be exempt from the U.S. federal withholding tax described above. To claim the exemption, the Non-U.S. Holder must furnish to the applicable withholding agent a valid IRS Form W-8ECI, certifying that the dividends are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States. Any such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular rates. A Non-U.S. Holder that is a corporation may also be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected dividends, as adjusted for certain items. Non-U.S. Holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

Sale or Other Taxable Disposition

A Non-U.S. Holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other taxable disposition of our common stock unless:

- the gain is effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such gain is attributable);
- the Non-U.S. Holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or
- our common stock constitutes a U.S. real property interest, or USRPI, by reason of our status as a U.S. real property holding corporation, or USRPHC, for U.S. federal income tax purposes.

Gain described in the first bullet point above generally will be subject to U.S. federal income tax on a net income basis at the regular rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

A Non-U.S. Holder described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on gain realized upon the sale or other taxable disposition of our common stock, which may be offset by U.S. source capital losses of the Non-U.S. Holder (even though the individual is not considered a resident of the United States), provided the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we currently are not, and do not anticipate becoming, a USRPHC. Because the determination of whether we are a USRPHC depends, however, on the fair market value of our USRPIs relative to the fair market value of our non-U.S. real property interests and our other business assets, there can be no assurance we are currently not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition of our common stock by a Non-U.S. Holder will not be subject to U.S. federal income tax if our common stock is "regularly traded," as defined by applicable Treasury Regulations, on an established securities market and such Non-U.S. Holder owned, actually and constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the Non-U.S. Holder's holding period.

Non-U.S. Holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

Payments of dividends on our common stock will not be subject to backup withholding, provided the applicable withholding agent does not have actual knowledge or reason to know the holder is a United States person and the holder either certifies its non-U.S. status, such as by furnishing a valid IRS Form W-8BEN, W-8BEN-E or W-8ECI, or otherwise establishes an exemption. However, information returns are required to be filed with the IRS in connection with any distributions on our common stock paid to the Non-U.S. Holder, regardless of whether such distributions constitute dividends or whether any tax was actually withheld.

In addition, proceeds of the sale or other taxable disposition of our common stock within the United States or conducted through certain U.S.-related brokers generally will not be subject to backup withholding or information reporting if the applicable withholding agent receives the certification described above and does not have actual knowledge or reason to know that such holder is a United States person or the holder otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker generally will not be subject to backup withholding or information reporting.

Copies of information returns that are filed with the IRS may also be made available under the provisions of an applicable treaty or agreement to the tax authorities of the country in which the Non-U.S. Holder resides or is established.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a Non-U.S. Holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional Withholding Tax on Payments Made to Foreign Accounts

Withholding taxes may be imposed under Sections 1471 to 1474 of the Code (such Sections commonly referred to as the Foreign Account Tax Compliance Act, or FATCA) on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends on, or (subject to the proposed Treasury Regulations discussed below) gross proceeds from the sale or other disposition of, our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in clause (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends on our common stock. While withholding under FATCA would have applied also to payments of gross proceeds from the sale or other disposition of our common stock on or after January 1, 2019, proposed Treasury Regulations eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued.

Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock.

PLAN OF DISTRIBUTION

We have entered into an equity distribution agreement with Goldman Sachs & Co. LLC as our sales agent under which we may offer and sell from time to time our common stock having an aggregate offering price of up to $75.0 million. The sales agent may act as agent on our behalf or purchase shares of our common stock as principal.

Sales, if any, of common stock under the equity distribution agreement may be made in ordinary brokers' transactions, to or through a market maker, on or through the Nasdaq Global Select Market or any other market venue where the securities may be traded, in the over-the-counter market, in privately negotiated transactions, or through a combination of any such methods of sale. The sales agent may also sell our common stock by any other method permitted by law.

The securities may be sold at market prices prevailing at the time of sale, at prices related to such prevailing market prices or at negotiated prices.

We will designate the maximum amount of common stock to be sold through the sales agent on a daily basis or otherwise as we and the sales agent agree and the minimum price per share at which such common stock may be sold. Subject to the terms and conditions of the equity distribution agreement, the sales agent will use its reasonable efforts consistent with its normal sales and trading practices to sell on our behalf all of the designated shares of common stock. We may instruct the sales agent not to sell any common stock if the sales cannot be effected at or above the price designated by us in any such instruction. We or the sales agent, with respect to itself only, may suspend the offering of our common stock by notifying the other party.

The sales agent will provide to us written confirmation following the close of trading on the Nasdaq Global Select Market each day on which shares of common stock are sold under the equity distribution agreement. Each confirmation will include the number of shares of common stock sold on such day, the gross sales proceeds and the compensation payable by us to the sales agent. We will report at least quarterly the number of shares of common stock sold through the sales agent under the equity distribution agreement, the net proceeds to us (before expenses) and the compensation paid by us to the sales agent in connection with the sales of the shares of common stock.

We will pay the sales agent a commission of up to 3.0% of the gross sales price per share of common stock sold through such agent under the equity distribution agreement. We have also agreed to reimburse the sales agent for certain of their expenses.

Settlement of any sales of common stock will occur on the second business day following the date on which such sales were made (or such earlier day as is industry practice for regular-way trading). There is no arrangement for funds to be received in an escrow, trust or similar arrangement. Sales of our common stock as contemplated in this prospectus supplement will be settled through the facilities of The Depository Trust Company or by such other means as we and the sales agent may agree.

The offering of our common stock pursuant to the equity distribution agreement will terminate upon the earlier of (i) the sale of all of our shares of common stock subject to the equity distribution agreement, or (ii) termination of the equity distribution agreement by us or by the sales agent as provided therein.

In connection with the sale of the shares of common stock on our behalf, the sales agent may be deemed to be an "underwriter" within the meaning of the Securities Act, and the compensation paid to the sales agent may be deemed to be underwriting commissions or discounts.

We have agreed to provide indemnification and contribution to the sales agent against certain liabilities, including civil liabilities under the Securities Act.

LEGAL MATTERS

The validity of the shares of common stock offered hereby will be passed upon for us by Latham & Watkins LLP. Certain legal matters will be passed upon for the sales agent by Ropes & Gray LLP.

EXPERTS

The consolidated financial statements of bluebird bio, Inc. ("the Company") appearing in the Company's Annual Report (Form 10-K) for the year ended December 31, 2021, and the effectiveness of the Company's internal control over financial reporting as of December 31, 2021, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their reports thereon (which contains an explanatory paragraph describing conditions that raise substantial doubt about the Company's ability to continue as a going concern as described in Note 1 to the consolidated financial statements) included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the reports of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We file reports, proxy statements and other information with the SEC. Information filed with the SEC is available on the SEC's website at http://www.sec.gov.

We are subject to the information reporting requirements of the Exchange Act, and we have filed and will file reports, proxy statements and other information with the SEC. These reports, proxy statements and other information are available on the SEC's website at http://www.sec.gov. We also maintain a website at www.bluebirdbio.com, at which you may access these materials free of charge as soon as reasonably practicable after they are electronically filed with, or furnished to, the SEC. The information contained in, or that can be accessed through, our website is not part of, and is not incorporated into, this prospectus supplement.

This prospectus supplement is part of a registration statement that we filed with the SEC and does not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. Statements in this prospectus supplement and the accompanying prospectus about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website or our website, as provided above.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement. Information in this prospectus supplement supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus supplement. We incorporate by reference into this prospectus supplement and the registration statement of which this prospectus supplement and the accompanying prospectus is a part the information or documents listed below that we have filed with the SEC:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2021, filed with the SEC on March 4, 2022;
- the information specifically incorporated by reference into our Annual Report on Form 10-K from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on May 2, 2022;
- our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2022, filed with the SEC on May 9, 2022;
- our Current Reports on Form 8-K filed on January 18, 2022, February 4, 2022, March 4, 2022, March 7, 2022, March 31, 2022, April 5, 2022, May 2, 2022, June 7, 2022, June 10, 2022 and June 10, 2022, excluding, in each case, information "furnished" pursuant to Items 2.02, 7.01, or 9.01; and
- the description of our common stock contained in our registration statement on Form 8-A, filed with the SEC on June 14, 2013, including any amendment or report filed for the purpose of updating such description.

We are also incorporating by reference any future filings that we make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement.

Notwithstanding the statements in the preceding paragraphs, no document, report or exhibit (or portion of any of the foregoing) or any other information that we have "furnished" to the SEC pursuant to the Exchange Act shall be incorporated by reference into this prospectus supplement and the accompanying prospectus.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, including exhibits to these documents. You should direct any requests for documents either orally or in writing to:

bluebird bio, Inc.
455 Grand Union Boulevard
Somerville, MA 02145
Phone: (339) 499-9300
investor@bluebirdbio.com
Attn: Investor Relations

You also may access these filings on our website at www.bluebirdbio.com. We do not incorporate the information on our website into this prospectus supplement or the accompanying prospectus and you should not consider any information on, or that can be accessed through, our website as part of this prospectus supplement or any accompanying prospectus (other than those filings with the SEC that we specifically incorporate by reference into this prospectus supplement and the accompanying prospectus).

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus supplement will be deemed modified, superseded or replaced for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement modifies, supersedes or replaces such statement.

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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, and in one or more series, common stock, preferred stock, warrants, units, 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 4 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 February 18, 2020.

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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.

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, units, 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 and any accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in the accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. 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" or 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 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.

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, the "Exchange Act"), and, in accordance therewith, file annual, quarterly and special reports, proxy statements and other information with the SEC. These documents 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., 60 Binney Street, Cambridge, Massachusetts 02142, Attention: Secretary, or by telephone request to (339) 499-9300. Our website is located at *http://www.bluebirdbio.com*. Information contained on, or that can be accessed through, our website is not incorporated by reference into this prospectus and, therefore, is not part of this prospectus or any accompanying prospectus supplement.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus supplement is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below (File No. 001-35966) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (in each case, other than those documents or the portions of those documents deemed to be furnished and not be filed in accordance with SEC rules) between the date of this prospectus and the termination of this offering:

- Annual Report on Form 10-K for the year ended December 31, 2019, as filed with the SEC on February 18, 2020;
- Current Reports on Form 8-K, as filed with the SEC on January 13, 2020 (solely with respect to item 8.01 and the associated Item 9.01 (Exhibit 99.2)), and January 21, 2020; 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.

You may request a copy of these filings, at no cost, by contacting us, either orally or in writing, at:

bluebird bio, Inc.
60 Binney Street
Cambridge, Massachusetts 02142
Phone: (617) 245-2107
investor@bluebirdbio.com
Attn: Investor Relations

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.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This 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 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 "may," "will," "could," "should," "would," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue," 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 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 and drug product manufacturing capabilities;
- the timing or likelihood of regulatory filings and approvals for our product candidates;
- the timing or success of commercialization of our approved product and any future approved products;
- the pricing and reimbursement of our approved product and any future approved products;

- 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 approved product, 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 and licenses;
- our financial performance;
- developments relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under the caption "Risk Factors" in any documents incorporated by reference herein.

Given these uncertainties, you should not place undue reliance on these 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 that include forward-looking statements.

RISK FACTORS

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 our most recent annual report on Form 10-K which is on file with the SEC and is incorporated herein by reference, and other documents we file with the SEC that are deemed incorporated by reference into this prospectus.

ABOUT THE COMPANY

We are a biotechnology company committed to researching, developing, and commercializing potentially transformative gene therapies for severe genetic diseases and cancer. We have built an integrated product platform with broad therapeutic potential in a variety of indications based on our lentiviral gene addition platform, gene editing and cancer immunotherapy capabilities. We believe that gene therapy for severe genetic diseases has the potential to change the way patients living with these diseases are treated by addressing the underlying genetic defect that is the cause of their disease, rather than offering treatments that only address their symptoms. Our gene therapy programs include LentiGlobin for b-thalassemia; LentiGlobin for sickle cell disease, or SCD; and Lenti-D for cerebral adrenoleukodystrophy, or CALD. Our programs in oncology are focused on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies. bb2121 (idecabtagene vicleucel), and bb21217 are CAR-T cell product candidates for the treatment of multiple myeloma and partnered under our collaboration arrangement with Bristol-Myers Squibb.

In June 2019, we received conditional marketing approval from the European Commission for LentiGlobin gene therapy for b-thalassemia, being marketed in the European Union as ZYNTEGLO™ gene therapy (autologous CD34+ cells encoding bA-T87Q-globin gene), for patients 12 years and older with transfusion-dependent b-thalassemia, or TDT, who do not have a b^0/b^0 genotype, for whom hematopoietic stem cell, or HSC, transplantation is appropriate, but a human leukocyte antigen-matched, or HLA, related HSC donor is not available. We have begun commercializing ZYNTEGLO in the European Union and expect to begin generating product revenue in the first half of 2020. In the fourth quarter of 2019, we initiated rolling submission of a biologics license application, or BLA, to the U.S. Food and Drug Administration, or FDA, for regulatory approval of LentiGlobin for b-thalassemia in the United States for the treatment of patients with TDT who do not have a b^0/b^0 genotype. We are engaged with the FDA in discussions regarding the requirements and timing for providing certain information regarding various release assays for LentiGlobin for b-thalassemia, and subject to these ongoing discussions, we are currently planning to complete the BLA submission in the second half of 2020. We are engaged with the FDA and the European Medicines Agency, or EMA, in discussions regarding our proposed development plans for LentiGlobin for b-thalassemia in patients with TDT and b^0/b^0 genotypes.

We are currently developing LentiGlobin gene therapy for SCD in the United States and the European Union. We are engaged with the FDA and EMA in discussions regarding our proposed development plans, and anticipate a potential first submission in 2022 for marketing approval of LentiGlobin for the treatment of patients with SCD on the basis of clinical data from our ongoing HGB-206 and HGB-210 studies.

We are currently developing Lenti-D gene therapy for CALD in the United States and the European Union. Based on our discussions with the FDA and EMA, we believe that we may be able to seek approval for our Lenti-D gene therapy for the treatment of patients with CALD on the basis of clinical data from our ongoing Starbeam study, and the completed ALD-103 observational study. We anticipate a potential first submission in 2020 for marketing approval of our Lenti-D gene therapy for the treatment of patients with CALD.

In collaboration with Bristol-Myers Squibb, or BMS, we are developing bb2121 (idecabtagene vicleucel, or ide-cel) and bb21217 product candidates as treatments for multiple myeloma. We are co-developing and co-promoting ide-cel in the United States with BMS and we have exclusively licensed to BMS the development and commercialization rights for ide-cel outside of the United States. We and BMS anticipate a potential first submission in the first half of 2020 for marketing approval of ide-cel as a treatment for relapsed and refractory multiple myeloma. We have exclusively licensed the development and commercialization rights for the bb21217 product candidate to BMS, with an option for us to elect to co-develop and co-promote bb21217 within the United States.

We also have the following programs to discover and develop T cell product candidates to treat hematologic and solid tumor malignancies: acute myeloid leukemia, Merkel cell carcinoma, diffuse large B-cell lymphoma, and MAGE-A4 positive solid tumors. In the field of severe genetic diseases, we have a preclinical program for a gene therapy to treat mucopolysaccharidosis type I (MPSI), a genetic ultra-rare metabolic condition that causes severe neurologic impairment and organ damage.

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 60 Binney Street, Cambridge, Massachusetts 02142 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.”

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.

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.

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.

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.

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.

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 ale, 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.

LEGAL MATTERS

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

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019, and the effectiveness of our internal control over financial reporting as of December 31, 2019, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

bluebird bio, Inc.

Up to $75,000,000

Common Stock

PROSPECTUS SUPPLEMENT

June 22, 2022

Goldman Sachs & Co. LLC

Calculation of Filing Fee Tables

424(b)(5)
(Form Type)

bluebird bio, Inc.
(Exact Name of Registrant as Specified in its Charter)

Table 1: Newly Registered and Carry Forward Securities

	Security Type	Security Class Title	Fee Calculation or Carry Forward Rule	Amount Registered	Proposed Maximum Offering Price Per Unit	Maximum Aggregate Offering Price	Fee Rate	Amount of Registration Fee
Newly Registered Securities								
Fees to Be Paid	Equity	Common Stock, $0.01 par value per share	457(o)(1)	$75,000,000	—	$75,000,000	0.0000927	$6,952.50
Fees Previously Paid	—	—	—	—	—	—	—	—
	Total Offering Amounts					$75,000,000		$6,952.50
	Total Fees Previously Paid							—
	Total Fee Offsets							—
	Net Fee Due							$6,952.50

(1) The registration fee is calculated in accordance with Rule 457(o) under the Securities Act of 1933, as amended (the "Securities Act"), based on the proposed maximum aggregate offering price, and Rule 457(r) under the Securities Act. In accordance with Rules 456(b) and 457(r) under the Securities Act, the registrant initially deferred payment of all of the registration fee for the Registration Statement on Form S-3ASR (File No. 333-236489) filed by the registrant with the Securities and Exchange Commission on February 18, 2020.