UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): August 17, 2022

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bluebird bio, Inc.

(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-35966**	**13-3680878**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

455 Grand Union Boulevard, Somerville, MA	**02145**
(Address of Principal Executive Offices)	**(Zip Code)**

(339) 499-9300
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instructions A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.01 par value per share	BLUE	The NASDAQ Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On August 17, 2022, bluebird bio, Inc. ("bluebird bio" or the "Company") announced that the U.S. Food and Drug Administration (FDA) has approved ZYNTEGLO® (betibeglogene autotemcel), also known as beti-cel, a one-time gene therapy custom-designed to treat the underlying genetic cause of beta-thalassemia in adult and pediatric patients who require regular red blood cell (RBC) transfusions.

Also on August 17, 2022, following the FDA approval of ZYNTEGLO® bluebird bio announced further details of its U.S. commercialization plans for ZYNTEGLO.

The full text of the Company's press releases regarding these announcements are filed as Exhibits 99.1 and 99.2 to this Current Report on Form 8-K and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press release issued by bluebird bio, Inc. on August 17, 2022 (regarding FDA approval).
99.2	Press release issued by bluebird bio, Inc. on August 17, 2022 (regarding commercial launch).
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: August 17, 2022

bluebird bio, Inc.

By: /s/ Helen C. Fu

Name: Helen C. Fu

Title: Senior Vice President, General Counsel and Secretary

Exhibit 99.1

bluebird bio Announces FDA Approval of ZYNTEGLO®, the First Gene Therapy for People with Beta-Thalassemia Who Require Regular Red Blood Cell Transfusions

ZYNTEGLO offers potentially curative benefit across ages and genotypes, through the achievement of durable transfusion independence and normal or near normal total hemoglobin levels

Management team to host conference call Thursday, August 18 at 8:00 am ET

SOMERVILLE, Mass.--Aug. 17, 2022-- bluebird bio, Inc. (Nasdaq: BLUE) today announced the U.S. Food and Drug Administration (FDA) has approved ZYNTEGLO® (betibeglogene autotemcel), also known as beti-cel, a one-time gene therapy custom-designed to treat the underlying genetic cause of beta-thalassemia in adult and pediatric patients who require regular red blood cell (RBC) transfusions.

"The FDA approval of ZYNTEGLO offers people with beta-thalassemia the possibility of freedom from burdensome regular red blood cell transfusions and iron chelation, and unlocks new possibilities in their daily lives," said Andrew Obenshain, chief executive officer, bluebird bio. "After more than a decade of research and clinical development, and through the perseverance of clinicians, patients, and their families, the approval of ZYNTEGLO marks a watershed moment for the field of gene therapy. As the first ex-vivo lentiviral vector gene therapy approved in the U.S. for the treatment of people with beta-thalassemia, we are ushering in a new era in which gene therapy has the potential to transform existing treatment paradigms for diseases that currently carry a lifelong burden of care."

Beta-thalassemia is a rare, genetic blood disease caused by mutations in the beta-globin gene and characterized by significantly reduced or absent adult hemoglobin production. Patients with the most severe form, sometimes called transfusion-dependent beta-thalassemia or beta-thalassemia major, experience severe anemia and lifelong dependence on regular red blood cell transfusions, a lengthy process that patients typically undergo every 2-5 weeks. Despite advances in treatment and improved transfusion techniques, transfusions only temporarily address symptoms of anemia and people with beta-thalassemia who require regular transfusions have an increased risk for morbidity and mortality due to complications from treatment-related iron overload. Data from the Cooley's Anemia Foundation indicate that the median age of death of patients with transfusion-dependent beta-thalassemia in the U.S. who died during the last decade was just 37 years. bluebird estimates that there are approximately 1,300-1,500 individuals with transfusion-dependent beta-thalassemia in the U.S.

"Transfusion-dependent beta-thalassemia is associated with an intense treatment burden and significant health risks related to regular red blood transfusions and iron management," said Alexis A. Thompson, MD, MPH, Chief of the Division of Hematology, Children's Hospital of Philadelphia. "As a clinician and an investigator in the ZYNTEGLO clinical development program, I celebrate the therapeutic potential of this treatment for patients and its implications for the field of gene therapy, all made possible through the incredible courage of patients and families who participated in the clinical trials."

"The Cooley's Anemia Foundation applauds the FDA's approval of ZYNTEGLO for people with beta-thalassemia who require regular red blood cell transfusions. The availability of a one-time gene therapy which offers the possibility of transfusion independence opens up new and exciting opportunities for those who are medically eligible to receive this treatment option," said Craig Butler, National Executive Director, Cooley's Anemia Foundation. "While advances in treatment have been of enormous benefit to those with beta-thalassemia, a potentially curative therapy may offer a true life-changing experience."

The approval of ZYNTEGLO is the culmination of nearly 10 years of clinical research of gene therapy in patients with transfusion-dependent beta-thalassemia. ZYNTEGLO works by adding functional copies of a modified form of the beta-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs) to allow them to make normal to near normal levels of total hemoglobin without regular RBC transfusions. The functional beta-globin gene is added into a patient's cells outside of the body (*ex-vivo*), and then infused into the patient. Though

ZYNTEGLO is designed to be administered to the patient once, the treatment process is comprised of several steps that may take place over the course of several months.

Due to the complex nature of gene therapy, ZYNTEGLO will be available exclusively at Qualified Treatment Centers (QTCs) which are carefully selected based on their expertise in relevant areas such as stem cell transplantation, cell and gene therapy, and beta-thalassemia; and receive specialized training to administer ZYNTEGLO. Information on bluebird's QTC network, as well as personalized support focused on the needs of each patient throughout their treatment journey and information on insurance coverage and access will be available through bluebird's patient support program, my bluebird support. Patients can call 833-888-NEST (833-888-6378) for more information, and additional details will be available at mybluebirdsupport.com in the coming days.

ZYNTEGLO was reviewed under Priority Review, and the Company received a Priority Review voucher upon approval. ZYNTEGLO was previously granted Orphan Drug designation and Breakthrough Therapy designation.

Clinical Data Supporting Approval of ZYNTEGLO
bluebird bio has the longest and most robust clinical program in transfusion-dependent beta-thalassemia (TDT) in the field of gene therapy. The approval of ZYNTEGLO is based on data from bluebird bio's Phase 3 studies HGB-207 (Northstar-2) and HGB-212 (Northstar-3), and the long-term follow-up study LTF-303.

The single-arm, open-label, 24-month Phase 3 studies of ZYNTEGLO included 41 patients aged 4 to 34 years with both non-β0/β0 and β0/β0 genotypes, with longest follow up out to 4 years. Eighty-nine percent (32/36) of evaluable patients across ages and genotypes achieved transfusion independence (TI), which is defined as no longer needing red blood cell transfusions for at least 12 months while maintaining a weighted average total hemoglobin of at least 9 g/dL. Results in these patients were durable as of last follow-up.

The most common non-laboratory adverse reactions (≥20%) were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. The most common Grade 3 or 4 laboratory abnormalities (>50%) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

Enrollment is complete and all patients have been treated in the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies evaluating ZYNTEGLO. Follow-up in HGB-212 is ongoing. bluebird bio is also conducting a long-term follow-up study, LTF-303, to monitor safety and efficacy for patients with TDT who have participated in bluebird bio-sponsored clinical studies of lentiviral vector (LVV) gene therapy through 15 years post-treatment. Across all studies, all patients who achieved transfusion independence have remained transfusion-free.

Investor Conference Call Information
bluebird bio will host a call for analysts and investors on Thursday, August 18, 2022, at 8:00 am ET. Please note that there is a new process to access the call via telephone. To register and receive a dial in number and unique PIN to access the live conference call, please follow this link https://register.vevent.com/register/BI7434d72a3e4344cd9d280e2d0825685e to register online.

The live webcast of the call and slide deck may be accessed by visiting the "Events & Presentations" page within the Investors & Media section of the bluebird website at http://investor.bluebirdbio.com. A replay of the webcast will be available on the bluebird website for 90 days following the event.

About ZYNTEGLO® (betibeglogene autotemcel) or beti-cel
ZYNTEGLO is a first-in-class, one-time ex-vivo LVV gene therapy approved for the treatment of beta-thalassemia in adult and pediatric patients who require regular red blood cell (RBC) transfusions. ZYNTEGLO works by adding functional copies of a modified form of the beta-globin gene (βA-T87Q-globin gene) into a patient's own hematopoietic (blood) stem cells to enable the production of a modified functional adult hemoglobin (HbAT87Q). Once a patient has the βA-T87Q-globin gene, they have the potential to increase ZYNTEGLO-derived adult hemoglobin (HbAT87Q) and total hemoglobin to normal or near normal levels that can eliminate the need for regular RBC transfusions.

Indication
ZYNTEGLO is indicated for the treatment of adult and pediatric patients with beta-thalassemia who require regular red blood cell (RBC) transfusions.

Important Safety Information

Delayed Platelet Engraftment
Delayed platelet engraftment has been observed with ZYNTEGLO treatment. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia; 15% of patients had ≥ Grade 3 decreased platelets on or after Day 100.

Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.

Risk of Neutrophil Engraftment Failure
There is a potential risk of neutrophil engraftment failure after treatment with ZYNTEGLO. Neutrophil engraftment failure is defined as failure to achieve three consecutive absolute neutrophil counts (ANC) ≥ 500 cells/microliter obtained on different days by Day 43 after infusion of ZYNTEGLO. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a patient treated with ZYNTEGLO, provide rescue treatment with the back-up collection of CD34+ cells.

Risk of Insertional Oncogenesis
There is a potential risk of LVV mediated insertional oncogenesis after treatment with ZYNTEGLO.

Patients treated with ZYNTEGLO may develop hematologic malignancies and should be monitored lifelong. Monitor for hematologic malignancies with a complete blood count (with differential) at Month 6 and Month 12 and then at least annually for at least 15 years after treatment with ZYNTEGLO, and integration site analysis at Months 6, 12, and as warranted.

In the event that a malignancy occurs, contact bluebird bio at 1 833-999-6378 for reporting and to obtain instructions on collection of samples for testing.

Hypersensitivity Reactions
Allergic reactions may occur with the infusion of ZYNTEGLO. The dimethyl sulfoxide (DMSO) in ZYNTEGLO may cause hypersensitivity reactions, including anaphylaxis.

Anti-retroviral and Hydroxyurea
Use Patients should not take prophylactic HIV anti-retroviral medications or hydroxyurea for at least one month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed. If a patient requires anti-retrovirals for HIV prophylaxis, then confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.

Interference with Serology Testing
Patients who have received ZYNTEGLO are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a false-positive test for HIV. Therefore, patients who have received ZYNTEGLO should not be screened for HIV infection using a PCR-based assay.

Adverse Reactions
The most common non-laboratory adverse reactions (≥20%) were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation,

nausea, decreased appetite, pigmentation disorder, and pruritus. The most common Grade 3 or 4 laboratory abnormalities (>50%) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

Drug Interactions
Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. The prescribing information for the iron chelator(s) and the myeloablative conditioning agent should be consulted for the recommendations regarding co-administration with CYP3A substrates.

Some iron chelators are myelosuppressive. After ZYNTEGLO infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider administration of non-myelosuppressive iron chelators. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Pregnancy/Lactation
Advise patients of the risks associated with conditioning agents, including on pregnancy and fertility. ZYNTEGLO should not be administered to women who are pregnant, and pregnancy after ZYNTEGLO infusion should be discussed with the treating physician.

ZYNTEGLO is not recommended for women who are breastfeeding, and breastfeeding after ZYNTEGLO infusion should be discussed with the treating physician.

Females and Males of Reproductive Potential
A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before ZYNTEGLO administration.

Women of childbearing potential and men capable of fathering a child should use an effective method of contraception (intra uterine device or combination of hormonal and barrier contraception) from start of mobilization through at least 6 months after administration of ZYNTEGLO.

Advise patients of the option to cryopreserve semen or ova before treatment if appropriate.

Please see full Prescribing Information for ZYNTEGLO.

About bluebird bio, Inc.
bluebird bio is pursuing curative gene therapies to give patients and their families more bluebird days. With a dedicated focus on severe genetic diseases, bluebird has industry-leading clinical and research programs for sickle cell disease, beta-thalassemia and cerebral adrenoleukodystrophy and is advancing research to apply new technologies to these and other diseases. We custom design each of our therapies to address the underlying cause of disease and have developed in-depth and effective analytical methods to understand the safety of our lentiviral vector technologies and drive the field of gene therapy forward.

Founded in 2010, bluebird has the largest and deepest ex-vivo gene therapy data set in the world—setting the standard for industry. Today, bluebird continues to forge new paths, combining our real-world experience with a deep commitment to patient communities and a people-centric culture that attracts and grows a diverse flock of dedicated birds.

For more information, visit bluebirdbio.com or follow us on social media at @bluebirdbio, LinkedIn, Instagram and YouTube.

bluebird bio Cautionary Statement Regarding Forward-Looking Statements
This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be,

forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect bluebird bio's business, particularly those identified in the risk factors discussion in bluebird bio's Annual Report on Form 10-K, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. These risks and uncertainties include, but are not limited to: the risk that the efficacy and safety results from our prior and ongoing clinical trials will not continue or be seen in the commercial treatment context; the risk that additional insertional oncogenic or other safety events associated with lentiviral vector, drug product, or myeloablation will be discovered or reported over time; the risk that we may not be able to obtain adequate price and reimbursement for any approved products; the risk that we may encounter delays in the initiation of our commercial operations in the United States; and the risk that any one or more of our product candidates will not be successfully developed, approved by the FDA or commercialized. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, bluebird bio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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Exhibit 99.2

bluebird bio Announces U.S. Commercial Infrastructure to Enable Patient Access to ZYNTEGLO®, the First and Only FDA-Approved Gene Therapy for People with Beta-Thalassemia Who Require Regular Red Blood Cell Transfusions

Price of ZYNTEGLO reflects potentially curative clinical benefit through achievement of durable transfusion independence and normal or near normal total hemoglobin levels

Innovative outcomes-based contract offering includes single upfront payment and up to 80% risk-sharing

ZYNTEGLO will be available through a network of Qualified Treatment Centers with experience delivering novel cell and gene therapies

"my bluebird support" patient services program will provide comprehensive, personalized support for patients and their families

SOMERVILLE, Mass., August 17, 2022—Following the FDA approval of ZYNTEGLO® (betibeglogene autotemcel), also known as beti-cel, for the treatment of beta-thalassemia in adult and pediatric patients who require regular red blood cell (RBC) transfusions, today bluebird bio released details of its U.S. commercial infrastructure to support rapid access to ZYNTEGLO, including an innovative, outcomes-based contract offering and a comprehensive patient support program.

"As the first and only FDA-approved gene therapy for people with beta-thalassemia who require regular red blood cell transfusions, and with the potential to untether patients from a lifelong, burdensome treatment regimen, ZYNTEGLO is setting the standard for what a one-time therapy can deliver," said Tom Klima, chief commercial and operating officer, bluebird bio. "We have developed an equally innovative commercial infrastructure in collaboration with payers and providers, and with a focus on patients, to enable broad and timely access to ZYNTEGLO for eligible patients and to support patients and families at every step of the treatment journey."

Under the current standard of care, patients with transfusion-dependent beta-thalassemia require RBC transfusions every two to five weeks and may lose decades of life relative to the general population. The lifetime cost of medical care for a patient with transfusion-dependent beta-thalassemia can reach up to $6.4 million in the U.S. and the average total health care cost per patient per year is 23 times higher than the general population. bluebird estimates that there are approximately 1,300-1,500 individuals with transfusion-dependent beta-thalassemia in the U.S.

bluebird has set the wholesale acquisition cost of ZYNTEGLO in the U.S. at $2.8M in recognition of its robust and sustained clinical benefit demonstrated in clinical studies and its potential to alleviate a lifetime of health care costs associated with regular RBC transfusions and iron management.

Payers Prepared to Support Access, Reimbursement

bluebird has devised an innovative strategy to enable timely and quality access to ZYNTEGLO, informed by payer insights and is committed to flexibility to meet payer needs. This includes one upfront payment that can be paired with an outcomes-based agreement. As part of this agreement, bluebird will reimburse contracted commercial and government payers up to 80% of the cost of the therapy if a patient fails to achieve and maintain transfusion independence up to two years following infusion. All patients in ZYNTEGLO Phase 3 studies who achieved transfusion independence (TI) have remained transfusion free. This outcomes measure is recognized by payers and providers as clinically meaningful and straightforward to track through claims data.

"A one-time therapy with the potential to free patients from chronic transfusions may change the lives of countless patients and their families and transform the treatment paradigm for transfusion-dependent beta-thalassemia," said Michael Sherman, MD, MBA, MS, executive vice president and chief medical officer of Point32Health. "Point32Health is thrilled to collaborate with bluebird bio to provide access to this first-of-its kind therapy for our

members who currently spend hundreds of hours each year managing their disease. bluebird's commitment to refunding up to 80 percent of the treatment cost meaningfully reduces the risk associated with an upfront payment, and will enable implementation of an outcomes-based agreement at a scale and magnitude not previously seen in the U.S."

Payers have expressed a deep understanding of the unmet need in transfusion-dependent beta-thalassemia, and the value of ZYNTEGLO. Approximately 70-75% of patients with transfusion-dependent beta-thalassemia are covered by commercial insurance, and bluebird is currently in late-stage negotiations with leading commercial payers including national Pharmacy Benefit Managers (PBMs) with the potential to represent dozens of plans. Additionally, we are engaging with state Medicaid agencies representing approximately 80% of publicly insured thalassemia patients.

Qualified Treatment Centers are Preparing for Patients
ZYNTEGLO will be available exclusively through bluebird Qualified Treatment Centers (QTCs)—leading healthcare institutions selected on the basis of clinical expertise in beta-thalassemia and other hemoglobinopathies, stem cell transplant, and cell and gene therapy—to best support the specialized nature of *ex-vivo* lentiviral vector gene therapy.

"Our network of Qualified Treatment Centers includes preeminent transplant institutions from across the U.S. and is committed to transforming the treatment of patients with beta-thalassemia who require regular red blood cell transfusions," said Richard Colvin, MD, chief medical officer, bluebird bio. "These Centers are critical partners in our mission for patients and were selected not only for their exceptional clinical expertise in treating patients with beta-thalassemia, but for their practical experience with the specialized manufacturing and novel reimbursement associated with one-time therapies."

The ZYNTEGLO QTC network includes established transplant centers from across the U.S. bluebird plans to onboard QTCs on a rolling basis, with the first wave of QTCs trained and activated in September 2022, in anticipation of initiating first patient apheresis in the fourth quarter.

More information on the ZYNTEGLO Qualified Treatment Center network will be available through *my bluebird support*.

***my bluebird support* Available to Assist Patients and Families at All Stages of the ZYNTEGLO Treatment Journey**
bluebird's patient support program, *my bluebird support*, will offer personalized support for patients and their families related to all aspects of the gene therapy journey—from education and resources to support informed decision-making to benefits verification and logistical support.

Patients and families interested in more information about ZYNTEGLO or who are beginning the treatment journey can contact *my bluebird support* to connect with an experienced Patient Navigator who can assist with:

- **Education** on the bluebird bio treatment process, how to find a Qualified Treatment Center, and questions about insurance and treatment planning
- **Insurance** questions including benefits verification, claims support, and co-pay assistance or other resources for eligible patients
- **Treatment** support at all phases of the gene therapy journey including logistical and financial support for eligible patients

"We recognize the decision to pursue gene therapy is complex and deeply personal, and that the treatment process can be a major undertaking for families. Our goal with *my bluebird support* is to provide comprehensive support services that are as customized as our therapies to enable a seamless experience for patients and their families," said Klima.

Patients and caregivers can call 833-888-NEST (833-888-6378) Monday-Friday between 8 a.m. and 8 p.m. Eastern to ask questions and enroll. More information will be available at mybluebirdsupport.com in the coming days.

ZYNTEGLO Clinical Data
bluebird bio has the longest and most robust clinical program in transfusion-dependent beta-thalassemia (TDT) in the field of gene therapy. The approval of ZYNTEGLO is based on data from bluebird bio's Phase 3 studies HGB-207 (Northstar-2) and HGB-212 (Northstar-3), and the long-term follow-up study LTF-303.

The single-arm, open-label, 24-month Phase 3 studies of ZYNTEGLO included 41 patients aged 4 to 34 years with both non-β0/β0 and β0/β0 genotypes, with longest follow up out to 4 years. Eighty-nine percent (32/36) of evaluable patients across ages and genotypes achieved transfusion independence (TI), which is defined as no longer needing RBC transfusions for at least 12 months while maintaining a weighted average total hemoglobin of at least 9 g/dL. Results in these patients were durable as of last follow-up.

The most common non-laboratory adverse reactions (≥20%) were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. The most common Grade 3 or 4 laboratory abnormalities (>50%) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

Enrollment is complete and all patients have been treated in the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies evaluating ZYNTEGLO. Follow-up in HGB-212 is ongoing. bluebird bio is also conducting a long-term follow-up study, LTF-303, to monitor safety and efficacy for patients with TDT who have participated in bluebird bio-sponsored clinical studies of lentiviral vector (LVV) gene therapy through 15 years post-treatment.

Across all studies, all patients who achieved transfusion independence have remained transfusion-free.

About ZYNTEGLO® (betibeglogene autotemcel) or beti-cel
ZYNTEGLO is a first-in-class, one-time ex-vivo LVV gene therapy approved for the treatment of beta-thalassemia in adult and pediatric patients who require regular red blood cell transfusions. ZYNTEGLO works by adding functional copies of a modified form of the beta-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient's own hematopoietic (blood) stem cells to enable the production of a modified functional adult hemoglobin (HbA^{T87Q}). Once a patient has the $\beta^{A\text{-}T87Q}$-globin gene, they have the potential to increase ZYNTEGLO-derived adult hemoglobin (HbA^{T87Q}) and total hemoglobin to normal or near normal levels that can eliminate the need for regular red blood cell (RBC) transfusions.

Indication
ZYNTEGLO is indicated for the treatment of adult and pediatric patients with beta-thalassemia who require regular red blood cell (RBC) transfusions.

Important Safety Information

Delayed Platelet Engraftment
Delayed platelet engraftment has been observed with ZYNTEGLO treatment. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia; 15% of patients had ≥ Grade 3 decreased platelets on or after Day 100.

Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.

Risk of Neutrophil Engraftment Failure
There is a potential risk of neutrophil engraftment failure after treatment with ZYNTEGLO. Neutrophil engraftment failure is defined as failure to achieve three consecutive absolute neutrophil counts (ANC) ≥ 500 cells/microliter obtained on different days by Day 43 after infusion of ZYNTEGLO. Monitor neutrophil counts until engraftment has

been achieved. If neutrophil engraftment failure occurs in a patient treated with ZYNTEGLO, provide rescue treatment with the back-up collection of CD34+ cells.

Risk of Insertional Oncogenesis
There is a potential risk of LVV mediated insertional oncogenesis after treatment with ZYNTEGLO.

Patients treated with ZYNTEGLO may develop hematologic malignancies and should be monitored lifelong. Monitor for hematologic malignancies with a complete blood count (with differential) at Month 6 and Month 12 and then at least annually for at least 15 years after treatment with ZYNTEGLO, and integration site analysis at Months 6, 12, and as warranted.

In the event that a malignancy occurs, contact bluebird bio at 1 833-999-6378 for reporting and to obtain instructions on collection of samples for testing.

Hypersensitivity Reactions
Allergic reactions may occur with the infusion of ZYNTEGLO. The dimethyl sulfoxide (DMSO) in ZYNTEGLO may cause hypersensitivity reactions, including anaphylaxis.

Anti-retroviral and Hydroxyurea Use
Patients should not take prophylactic HIV anti-retroviral medications or hydroxyurea for at least one month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed. If a patient requires anti-retrovirals for HIV prophylaxis, then confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.

Interference with Serology Testing
Patients who have received ZYNTEGLO are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a false-positive test for HIV. Therefore, patients who have received ZYNTEGLO should not be screened for HIV infection using a PCR-based assay.

Adverse Reactions
The most common non-laboratory adverse reactions (≥20%) were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. The most common Grade 3 or 4 laboratory abnormalities (>50%) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

Drug Interactions
Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. The prescribing information for the iron chelator(s) and the myeloablative conditioning agent should be consulted for the recommendations regarding co-administration with CYP3A substrates.

Some iron chelators are myelosuppressive. After ZYNTEGLO infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider administration of non-myelosuppressive iron chelators. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Pregnancy/Lactation
Advise patients of the risks associated with conditioning agents, including on pregnancy and fertility. ZYNTEGLO should not be administered to women who are pregnant, and pregnancy after ZYNTEGLO infusion should be discussed with the treating physician.

ZYNTEGLO is not recommended for women who are breastfeeding, and breastfeeding after ZYNTEGLO infusion should be discussed with the treating physician.

Females and Males of Reproductive Potential
A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before ZYNTEGLO administration.

Women of childbearing potential and men capable of fathering a child should use an effective method of contraception (intra uterine device or combination of hormonal and barrier contraception) from start of mobilization through at least 6 months after administration of ZYNTEGLO.

Advise patients of the option to cryopreserve semen or ova before treatment if appropriate.

Please see full Prescribing Information for ZYNTEGLO.

About bluebird bio, Inc.
bluebird bio is pursuing curative gene therapies to give patients and their families more bluebird days. With a dedicated focus on severe genetic diseases, bluebird has industry-leading clinical and research programs for sickle cell disease, beta-thalassemia and cerebral adrenoleukodystrophy and is advancing research to apply new technologies to these and other diseases. We custom design each of our therapies to address the underlying cause of disease and have developed in-depth and effective analytical methods to understand the safety of our lentiviral vector technologies and drive the field of gene therapy forward.

Founded in 2010, bluebird has the largest and deepest *ex-vivo* gene therapy data set in the world—setting the standard for industry. Today, bluebird continues to forge new paths, combining our real-world experience with a deep commitment to patient communities and a people-centric culture that attracts and grows a diverse flock of dedicated birds.

For more information, visit bluebirdbio.com or follow us on social media at @bluebirdbio, LinkedIn, Instagram and YouTube.

bluebird bio Cautionary Statement Regarding Forward-Looking Statements
This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements, such as statements regarding the commercialization of ZYNTEGLO, including without limitation the likelihood of executing binding agreements with payers, our expectations on timing for activating QTCs, our expectations on the timing and size for expanding our QTC network, our plans for the first patient apheresed in the commercial setting, and the availability of services offered by my bluebird support program to support patient treatment. Such forward-looking statements are based on historical performance and current expectations and projections about our future goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect bluebird bio's business, particularly those identified in the risk factors discussion in bluebird bio's Annual Report on Form 10-K, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. These risks and uncertainties include, but are not limited to: the risk that the efficacy and safety results from our prior and ongoing clinical trials will not continue or be seen in the commercial context, including that patients do not achieve or maintain transfusion independence; the risk that we are not able to activate QTCs on the timeframe that we expect; the risk that the QTCs experience delays in their ability to enroll or treat patients; the risk that we experience delays in establishing operational readiness across our supply chain following approval to support treatment in the commercial context; the risk that there is not sufficient patient demand or payer reimbursement to support continued commercialization of ZYNTEGLO; the risk that additional insertional oncogenic or other safety events associated with lentiviral vector, drug product, or myeloablation will be discovered or reported over time;

and the risk that eli-cel or lovo-cel will not be successfully developed, approved by the FDA or commercialized. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, bluebird bio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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