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): December 11, 2021

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.)**
60 Binney Street, Cambridge, MA		**02142**
(Address of Principal Executive Offices)		**(Zip Code)**

Registrant's Telephone Number, Including Area Code: (339) 499-9300

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 December 11, 2021, bluebird bio, Inc. ("bluebird") issued a press release announcing new data presented at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition of its results for betibeglogene autotemcel (beti-cel), an investigational gene therapy, that demonstrate adult and pediatric patients living with β-thalassemia (beta-thal) who require regular red blood cell (RBC) transfusions can produce normal or near-normal levels of total hemoglobin and continue to remain transfusion-free, and achieve stable iron markers, through up to seven years of follow-up. Data from the pivotal HGB-207 Northstar-2 study were also published in the *New England Journal of Medicine* (NEJM).

On December 12, 2021, bluebird issued a press release announcing data presented at ASH with results from its Phase 1/2 HGB-206 study of lovotibeglogene autotemcel (lovo-cel; formerly LentiGlobin for SCD, bb1111) gene therapy for adult and adolescent patients with sickle cell disease, including further analyses from its pivotal cohort, HGB-206 Group C, following enhancements to the manufacturing protocols and treatment process. Select data from the Group C cohort of the HGB-206 study were simultaneously published in NEJM.

The full text of bluebird'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 December 11, 2021 (regarding beti-cel data).
99.2	Press release issued by bluebird bio, Inc. on December 12, 2021 (regarding lovo-cel data).
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: December 13, 2021

bluebird bio, Inc.

By: /s/ Helen C. Fu

Helen C. Fu

Senior Vice President, General Counsel and Secretary

Exhibit 99.1

New Data at ASH21 and Published in *NEJM* Further Demonstrate beti-cel as a Potentially Curative One-Time Gene Therapy for β-thalassemia in Patients Who Require Regular Transfusions Through the Achievement of Durable Transfusion Independence and Normal or Near-Normal Adult Hemoglobin Levels

Oral presentation featured in the ASH press program includes long-term data through August 2021 in patients who achieved transfusion independence (TI) (n=46) and remain transfusion-free through up to seven years of follow-up

beti-cel stabilized iron markers in patients who achieved TI and were able to stop iron chelation (n=20/34), with markers of iron management improving toward normal

Adult, adolescent and pediatric patients experienced early and sustained improvement in health-related quality-of-life measures from baseline across Phase 3 studies

CAMBRIDGE, Mass.— (BUSINESS WIRE) — December 11, 2021—bluebird bio, Inc. (Nasdaq: BLUE) today presented new results for betibeglogene autotemcel (beti-cel), a deeply studied investigational gene therapy, that demonstrate adult and pediatric patients living with β-thalassemia (beta-thal) who require regular red blood cell (RBC) transfusions can produce normal or near-normal levels of total hemoglobin and continue to remain transfusion-free, and achieve stable iron markers, through up to seven years of follow-up (n=3). These findings further support beti-cel as a potentially curative one-time treatment option that addresses the underlying genetic cause of beta-thal and mitigates the burdens associated with the practical management of the disease. The data were highlighted in the press program and will be delivered in an oral presentation at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition, taking place December 11-14, 2021, at the Georgia World Congress Center in Atlanta and virtually. Data from the pivotal HGB-207 Northstar-2 study were also simultaneously published in an original article in *The New England Journal of Medicine (NEJM)* titled, “Betibeglogene Autotemcel Gene Therapy for Non-β0/β0 Genotype β-Thalassemia.”

“It is encouraging to see the results presented at ASH today showing that beti-cel is potentially curative for patients with β-thalassemia who require regular red blood cell transfusions, and which build on the strong evidence collected over seven years in this clinical program,” said Alexis A. Thompson, MD, MPH, Hematology Section Head, Ann & Robert H. Lurie Children’s Hospital of Chicago. “beti-cel enables the production of healthy adult hemoglobin, which may offer patients freedom from lifelong red blood cell transfusions. Restoring iron homeostasis is also crucial to any person’s journey with beta-thal, as iron overload can result from transfusions, as well as increased intestinal iron absorption due to ineffective red blood cell production. The majority of patients treated with beti-cel who achieved transfusion independence were able to stop iron chelation (or removal), and stabilization of iron markers was sustained even after chelation was discontinued.”

Transfusion-dependent beta-thal is a severe genetic disease caused by mutations in the β-globin gene, which may cause significantly reduced or absent adult hemoglobin (Hb) production. This can result in severe anemia and lifelong dependence on RBC transfusions, a lengthy process that patients typically undergo every 3-4 weeks. Despite advances in treatment and improved transfusion techniques, transfusions only temporarily address symptoms of anemia and people with beta-thal who require regular transfusions have an increased risk for morbidity and mortality due to treatment- and disease-related iron overload and its complications.

beti-cel is a one-time gene therapy that adds functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient’s own hematopoietic (blood) stem cells (HSCs). Once patients have the $\beta^{A\text{-}T87Q}$-globin gene, the HSCs have the potential to produce gene therapy-derived adult Hb (HbA^{T87Q}) at levels that can eliminate the need for transfusions. In studies of beti-cel, transfusion independence is

defined as no longer needing RBC transfusions for at least 12 months while maintaining a weighted average Hb of at least 9 g/dL.

“These important new data build on a robust body of clinical evidence to reinforce the curative potential of beti-cel for patients and families living with β-thalassemia, a disease for which treatment advances are urgently needed,” said Richard Colvin, MD, PhD, chief medical officer, bluebird bio. “Beti-cel addresses the underlying genetic cause of beta-thal in patients who require regular transfusions, enabling the stable production of adult hemoglobin and demonstrating sustained improvement in clinical outcomes through the longest available follow-up in the field. The robust, long-term clinical data in the beti-cel development program enable us to observe the truly transformative difference in people’s lives that transfusion independence provides.”

As of the data cut-off of August 18, 2021, a total of 63 pediatric, adolescent and adult patients, including 20 patients with at least five years of follow-up, 11 with at least six years and three with up to seven years across β^0/β^0 and non-β^0/β^0 genotypes, have been treated with beti-cel in the Phase 1/2 HGB-204 (Northstar) and HGB-205 studies and the Phase 3 HGB-207 (Northstar-2) and HGB-212 (Northstar-3) studies. Data from bluebird bio’s Phase 1/2 and Phase 3 clinical studies represent more than 240 patient-years of experience with beti-cel and the longest available follow-up data in beta-thal patients requiring regular RBC transfusions treated with one-time gene therapy.

“In the analysis published in *NEJM*, 91% of patients, including six of seven patients under the age of 12, achieved transfusion independence as well as improvement in erythropoiesis and liver iron concentrations,” said Professor Franco Locatelli, MD, PhD, lead author and Director, Department of Pediatric Hematology/Oncology and Cell and Gene Therapy, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy. “These findings are further validated with long-term data being presented at ASH, which suggest that one-time gene therapy with beti-cel is potentially curative through achievement of transfusion independence and near normal hemoglobin levels.”

Adverse reactions considered related to beti-cel were few and consisted primarily of non-serious infusion-related reactions that occurred on the day of infusion (e.g., abdominal pain, hot flush, dyspnea, tachycardia and non-cardiac chest pain) and cytopenias (e.g. thrombocytopenia, leukopenia and neutropenia). Pain in extremity shortly after treatment was also documented. One of these adverse events (AE) was a serious adverse event (SAE) of thrombocytopenia considered possibly related to beti-cel and has resolved.

The majority of AEs and SAEs in the beti-cel clinical development program were unrelated to beti-cel and consistent with the known side effects of HSC collection and busulfan conditioning regimen (including several SAEs of veno-occlusive disease that resolved with treatment).

Updated Long-Term Efficacy & Safety Results (Long-term follow-up study, LTF-303)
After participating in and completing the two years of follow-up in any of the Phase 1/2 (HGB-204, HGB-205) or Phase 3 studies (HGB-207, HGB-212), patients treated with beti-cel were invited to enroll in a 13-year long-term follow-up study, LTF-303.

As of August 18, 2021, 57 of 63 beti-cel-treated patients across age groups and genotypes spanning a broad range of the most severe β^0/β^0 and non-β^0/β^0 genotypes were enrolled in LTF-303 (22 treated in Phase 1/2 studies, 35 treated in Phase 3 studies) with a median post-infusion follow-up of 41.5 months (min-max: 23-87.5). Twenty patients enrolled in LTF-303 have at least five years of follow-up.

Transfusion Independence (TI)
Of the 57 patients enrolled in LTF-303, 46 patients achieved TI: 15/22 (68%) patients treated in Phase 1/2 and 31/35 (89%) patients treated in Phase 3. All 46 patients who achieved TI maintained it through last follow-up in LTF-303, demonstrating the long-term durability of beti-cel.

Phase 1/2 patients had a median duration of ongoing TI of 65.9 months (min-max: 19.8-84.5) and Phase 3 patients had a median ongoing TI duration of 32 months (min-max: 18.2-49.1).

Weighted average Hb in patients who achieved TI reached normal or near-normal levels in the Phase 1/2 studies (10.3 g/dL; min-max: 9.1-13.2) and in the Phase 3 studies (11.6 g/dL; min-max: 9.5-13.7).

Iron Marker Stabilization
Patients who require regular blood transfusions need to reduce excess iron caused by chronic blood transfusions. For people living with beta-thal, iron can be removed from the body in several ways, including chelation (pharmacological removal).

Prior to beti-cel infusion, all patients were on iron chelation. Importantly, the majority of patients who achieved TI (n=46/57) that restarted iron chelation after infusion have since stopped (59%, 20/34); and 24% of those who achieved TI (11/46) were able to receive phlebotomy (blood removal), which is another method for iron reduction that is only possible for patients who have sufficient hemoglobin levels without RBC transfusions. This supports the potential for beti-cel to reduce the treatment burden associated with iron management.

A sub-analysis of iron status in LTF-303 included 16 patients who achieved TI and stopped chelation, with at least nine months of follow-up after discontinuation of chelation. The sub-analysis showed iron reduction in response to chelation and stabilization of iron markers after chelation was discontinued.

LTF-303 Safety
There were no deaths, no vector-derived replication-competent lentivirus, and no events of insertional oncogenesis or malignancy in LTF-303.

No drug-related AEs were reported. Serious AEs unrelated to beti-cel included infertility issues (gonadotropic insufficiency, ectopic pregnancy, fetal death as a result of a miscarriage), gallbladder disease (gall bladder wall thickening/polyp), cholelithiasis, infection and low white blood cell count in the setting of a wild-type HIV (bacteremia, neutropenia), and individual events of diabetic ketoacidosis, pulmonary embolism, and major depression. Pulmonary embolism occurred concurrently with diabetic ketoacidosis in a patient with a history of thromboembolic events. Each event was reported once.

Health-Related Quality of Life (HRQoL)
“People with β-thalassemia live with increased morbidity and mortality and reduced health-related quality of life compared with the general population,” said Dr. Colvin. “The mental, physical, and time demands of regular, lifelong red blood cell transfusions, as well as iron chelation and associated complications, take a heavy toll on patients’ functioning in all spheres of life, including their work or school and social lives.[i] The robust, long-term clinical data in the beti-cel development program enable us to observe the truly transformative difference in people’s lives that transfusion independence provides.”

Measures of HRQoL were evaluated in adult (≥18 years of age) and pediatric/adolescent (<18 years of age) patients who achieved TI following treatment with beti-cel in the Phase 3 HGB-207 and HGB-212 studies and who completed baseline and one post-baseline self-reported HRQoL assessment. HRQoL was assessed at baseline and at Months 6, 12, 18, and 24 after beti-cel infusion, using multiple validated quality-of-life instruments.

Improvements in HRQoL outcomes were observed among patients across age groups and across multiple domains of physical and psychological health.

Clinically relevant improvements were observed, as measured by PedsQL and SF-36 scores at Month 24. Patients with scores below the population norm at baseline experienced the most improvement.

Additional HQRoL data will be presented at ASH in a poster titled, *Improvement in Health-Related Quality of Life Following Treatment with Betibeglogene Autotemcel in Patients with Transfusion-Dependent β-Thalassemia Enrolled in Phase 3 Studies*, on Monday, December 13. Results from the long-term LTF-303 study will be presented in detail in an oral presentation titled, *Restoring Iron Homeostasis in Patients who Achieved Transfusion Independence After Treatment with Betibeglogene Autotemcel Gene Therapy: Results from up to 7 Years of Follow-up*, on Monday, December 13 at 11:00 a.m. ET.

About betibeglogene autotemcel (beti-cel)
betibeglogene autotemcel (beti-cel) (pronounced BEH tee cell) is a one-time gene therapy custom-designed to treat the underlying cause of β-thalassemia in patients who require regular red blood cell (RBC) transfusions. Beti-cel adds functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs) in order to correct the deficiency of adult hemoglobin that is the hallmark of β-thalassemia. Once a patient has the modified β-globin gene, they have the potential to produce beti-cel-derived adult hemoglobin (HbA^{T87Q}) at levels that may eliminate the need for transfusions. In Phase 3 beti-cel studies 89% (31/35) of evaluable patients across ages and genotypes, including pediatric patients as young as four years of age and those with the most severe β^0/β^0 genotypes, achieved transfusion independence, which is defined as no longer needing RBC transfusions for at least 12 months while maintaining a weighted average Hb of at least 9 g/dL.

beti-cel is manufactured using the BB305 lentiviral vector (LVV), a third-generation, self-inactivating LVV that has been studied for more than a decade across two therapeutic areas.

Adverse reactions considered related to beti-cel consisted primarily of non-serious infusion-related reactions that occurred on the day of the infusion and cytopenias. One serious adverse event (SAE) of thrombocytopenia considered possibly related to beti-cel was reported and has resolved.

The majority of AEs and SAEs in the beti-cel clinical development program were considered to be unrelated to beti-cel by the Investigator and were consistent with known side effects of HSC collection and the bulsufan conditioning regimen.

The Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies evaluating beti-cel are ongoing; enrollment is complete, and all patients have been treated. bluebird bio is also conducting a long-term follow-up study, LTF-303, to monitor safety and efficacy for people who have participated in bluebird bio-sponsored beti-cel clinical studies through 15 years post treatment.

A biologics license application (BLA) for beti-cel is under priority review by the FDA. The agency has set a Prescription Drug User Fee Act (PDUFA) goal date of May 20, 2022.

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, β-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.

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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 financial results, 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 financial results, 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 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 additional patients treated with our product candidates; 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 any one or more of our product candidates will not be successfully developed, approved 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

New and Updated Data Demonstrating Sustained Treatment Response in Patients Treated in Largest Sickle Cell Gene Therapy Program To-Date presented at ASH21 and published in *NEJM*

Updated data from the pivotal cohort of HGB-206 reinforce that optimized manufacturing and treatment processes are associated with improved biologic and clinical outcomes, including stable production of gene therapy derived anti-sickling hemoglobin and continued complete resolution of severe VOEs up to 36 months follow-up (n=2)

Patient-reported data on health-related quality of life (HRQoL) complement clinical findings and the strongest HRQoL improvements in any sickle cell gene therapy program

CAMBRIDGE, Mass.— (BUSINESS WIRE) — December 12, 2021—bluebird bio, Inc. (NASDAQ: BLUE) today announced updated results from its Phase 1/2 HGB-206 study of lovotibeglogene autotemcel (lovo-cel; formerly LentiGlobin® for SCD, bb1111) gene therapy, including further analyses from its pivotal cohort, HGB-206 Group C, following enhancements to the manufacturing protocols and treatment process. In addition to continued complete resolution of severe vaso-occlusive events (VOEs), patients in Group C achieved near normal levels of key hemolysis markers and experienced sustained improvements in patient-reported quality of life following treatment. Data were presented in two oral sessions at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition, taking place December 11-14, 2021, at the Georgia World Congress Center in Atlanta, Georgia and virtually; select data from the Group C cohort of the HGB-206 study were simultaneously published in *New England Journal of Medicine*.

“Data presented at ASH and published today in the *New England Journal of Medicine* affirm that this lentiviral gene transfer for sickle cell disease has the potential to improve the day-to-day reality of people living with sickle cell disease by eliminating the disruptive, painful crises that can occur multiple times per month,” said John F. Tisdale, MD, Chief, Cellular and Molecular Therapeutics Branch, NHLBI, Bethesda, MD. “Sickle cell is a complex and often misunderstood disease that is associated with more symptoms and long-term effects than pain alone. It is encouraging to see that the treatment fundamentally impacted the pathophysiology of patients’ disease through the sustained production of vector-derived anti-sickling hemoglobin to substantially reduce sickling and hemolysis.”

Clinical studies evaluating lovo-cel in sickle cell disease represent the largest sickle cell disease gene therapy data set to date. As of February 17, 2021, 49 patients have been treated with lovo-cel with up to six years of patient follow-up (median: 24 months) across the HGB-205 (n=3), HGB-206 (n=44) and HGB-210 (n=2) clinical studies, representing more than 109 total patient-years of data. The Phase 1/2 HGB-206 trial includes Groups A (n=7), B (n=2) and C (n=35), reflecting progressive adaptations to the treatment and manufacturing processes.

Sickle cell disease is a serious, progressive and debilitating genetic disease caused by a single mutation in the β-globin gene that leads to the production of abnormal sickle hemoglobin (HbS). HbS causes red blood cells to become sickled and fragile, resulting in chronic hemolytic anemia, vasculopathy and unpredictable, painful VOEs requiring frequent hospitalization. In the U.S., the median age of death for someone with sickle cell disease is 43-46 years. Additionally, one in four people living with sickle cell disease experience a stroke by age 45.

In the HGB-206 study, VOEs are defined as episodes of acute pain with no medically determined cause other than a vaso-occlusion, lasting more than two hours and severe enough to require care at a medical facility. This includes acute episodes of pain, acute chest syndrome (ACS), acute hepatic sequestration and acute splenic sequestration. A severe VOE requires a 24-hour hospital stay or emergency room visit or at least two visits to a hospital or emergency room over a 72-hour period, with both visits requiring intravenous treatment.

lovo-cel adds functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient’s own hematopoietic (blood) stem cells (HSCs). Once patients have the $\beta^{A\text{-}T87Q}$-globin gene, their

red blood cells can produce anti-sickling hemoglobin (HbA^{T87Q}) that decreases the proportion of HbS, thereby reducing sickled red blood cells, hemolysis and other complications.

“The remarkable depth and breadth of data presented at ASH and published in the *New England Journal of Medicine* distinctively demonstrates the impact of lovo-cel on biologic and clinical outcomes, as well as to patient-reported outcomes that indicate a meaningful difference in the daily lives of people with sickle cell disease,” said Richard Colvin, MD, PhD, Chief Medical Officer, bluebird bio. “The ability to trace how lovo-cel integrates on a genetic level is a distinguishing characteristic of LVV gene therapy and confers a unique understanding of how the proposed mechanism of action of the drug product is correlated to safety and clinical outcomes.”

Data published in the *New England Journal of Medicine* can be found here: *Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease Gene Therapy*.

Updated HGB-206 Group C Efficacy & Safety Data
As of February 2021, the 35 Group C patients had up to 37.6 months of follow-up (median of 17.3; min-max: 3.7-37.6 months), for a total of 54.8 patient-years of experience.

Efficacy
Following engraftment, median total hemoglobin increased from 8.5 g/dL at baseline to ≥11 g/dL from six through up to 36 months post-infusion in all patients; notably, sickle hemoglobin (HbS) in all patients was less than 60% of total hemoglobin, and gene therapy-derived anti-sickling hemoglobin, HbA^{T87Q}, contributed at least 40% of total hemoglobin.

These decreased levels of sickle hemoglobin (HbS) after lovo-cel infusion were comparable to individuals living with sickle trait (β^S/β^A), not in the study– in general, people with sickle cell trait enjoy normal life spans with no medical problems related to sickle cell trait.

All evaluable patients (n=25) continued to experience complete resolution of severe VOEs through up to 36 months of follow-up, compared with a median of 3.5 per year (min–max: 2.0–13.5) in the 24 months before enrollment.

Hemolysis Markers
Red blood cells normally break down in the body through a naturally occurring process called hemolysis. In sickle cell disease, hemolysis happens too quickly due to the fragility of sickled red blood cells, resulting in hemolytic anemia. In findings published in *NEJM,* key hemolysis markers for sickle cell patients treated with lovo-cel in Group C approached normal levels.

From six months post-infusion through the last visit, several indicators of the health of red blood cells suggest that treatment with lovo-cel improved biological markers for SCD to near-normal levels. Lactate dehydrogenase and indirect bilirubin levels normalized, reticulocyte counts approached normal levels, and haptoglobin levels were positive at last visit, which suggests a reduction in hemolysis.

Pancellularity
Exploratory assay data evaluated HbA^{T87Q} and HbS protein in individual red blood cells to assess if HbA^{T87Q} was *pancellular,* meaning present throughout all of a patient’s red blood cells.

In 10 patients with at least 24 months of follow-up, a mean of 85% of red blood cells contained $\beta^{A\text{-}T87Q}$, suggesting near-pancellular HbA^{T87Q} distribution and with pancellularity further increasing over time. This indicates that there were very few circulating non-gene-therapy-modified RBCs containing a majority of HbS and prone to sickling. Within HbA^{T87Q}-containing red cells, the median HbA^{T87Q} was estimated to be 15.3 pg per red cell (range, 11.7 to 22.7), a finding that was similar to the range of 13 to 18 pg per cell of adult hemoglobin reported in persons with sickle cell trait.

Polyclonality
Lentiviral vector (LVV) gene therapy is uniquely traceable at the genetic level. Traceability is possible through the utilization of sophisticated and precise integration site analysis (ISA), which enables the active identification and tracking of LVV-modified cells after delivery to a patient, thereby improving the ability to further evaluate biological effects.

Based on manufacturing improvements reflected in the Group C cohort of HGB-206, greater diversity was detected in LVV insertion sites, which was associated with increased pancellularity, a reduced sickling rate, and reduced proliferative and hematopoietic stress.

Safety
There have been no reports of graft versus host disease (GvHD), graft failure, replication-competent lentivirus, or vector-mediated insertional oncogenesis in subjects from Group C or any subject treated in HGB-206.

The safety data from Group C patients in HGB-206 remain generally consistent with the known side effects of autologous hematopoietic stem cell collection and myeloablative single-agent busulfan conditioning, as well as underlying SCD. One non-serious, Grade 2 adverse event (AE) of febrile neutropenia was considered related to lovo-cel; additionally, one non-serious, Grade 2 AE of leukopenia and one Grade 1 AE of decreased diastolic blood pressure were considered possibly related to lovo-cel. There were no serious AEs related to lovo-cel.

As previously reported, one patient with significant baseline SCD-related cardiopulmonary disease died 20 months post-treatment; the treating physician and an independent monitoring committee agreed his death was unlikely related to lovo-cel and that SCD-related cardiac and pulmonary disease contributed.

In the initial cohort (Group A) of the HGB-206 study, two patients treated with lovo-cel developed acute myeloid leukemia (AML). After thorough investigations into the cases bluebird bio determined that these were unlikely related to the insertion of bluebird's lentiviral vector (LVV) gene therapy for SCD.

Patient-Reported Quality of Life
Sickle cell disease is characterized by high morbidity and early mortality. The management of such a complex disease with many sequalae has a profound impact on all aspects of patient quality of life—physical, mental and socioemotional.

Health-related quality of life (HRQoL) findings in Group C patients were generated using the Patient Reported Outcomes Measurement Information System 57 (PROMIS-57), a validated instrument in SCD.
Generally, improvements reported previously at Month 12 post infusion were sustained through Month 24. Specifically, 67% (n=10/15) reported a significant decrease in pain intensity at Month 12, which was sustained for 56% (n=5/9) of evaluable patients at Month 24. Similarly, 56% (n=9/16) reported clinically meaningful reductions in pain interference on daily life at Month 12, which was sustained at Month 24 (56%, 5/9). The majority of patients at Months 12 (69%, n=11/16) and Month 24 (63%, n=5/8) reported clinically meaningful improvements in physical functioning, and half of patients at Months 12 (50%, n=8/16 and 24 (56%, n=5/9) reported clinically meaningful reductions in fatigue following treatment with lovo-cel. The remaining domains reported trends toward improvement in other aspects of quality of life, including mental and social health.

These findings provide a broader understanding of the impact to patient life over time following treatment with lovo-cel and are the strongest HRQoL improvements reported to-date in the SCD treatment landscape.

About HGB-206
HGB-206 is an ongoing, Phase 1/2 open-label study designed to evaluate the efficacy and safety of lovo-cel gene therapy for sickle cell disease that includes three treatment cohorts: Groups A (n=7), B (n=2) and C (n=35). A refined manufacturing process designed to increase vector copy number (VCN) and

further protocol refinements made to improve engraftment potential of gene-modified stem cells were used for Group C. Group C patients also received lovo-cel made from HSCs collected from peripheral blood after mobilization with plerixafor, rather than via bone marrow harvest, which was used in Groups A and B of HGB-206.

Under a Cooperative Research and Development Agreement (CRADA), the National Heart, Lung, and Blood Institute, part of the National Institutes of Health, assisted bluebird in conducting clinical trials of its investigational LentiGlobin® gene therapy.

About lovotibeglogene autotemcel (lovo-cel; formerly LentiGlobin® for SCD, bb1111)
lovotibeglogene autotemcel (lovo-cel) gene therapy is an investigational one-time treatment being studied for sickle cell disease (SCD), that is designed to add functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs). Once patients have the $\beta^{A\text{-}T87Q}$-globin gene, their red blood cells can produce anti-sickling hemoglobin (HbA^{T87Q}) that decreases the proportion of HbS, with the goal of reducing sickled red blood cells, hemolysis and other complications. bluebird bio's clinical development program for lovo-cel includes the completed Phase 1/2 HGB-205 and ongoing Phase 1/2 HGB-206 and Phase 3 HGB-210 studies. bluebird bio is also conducting a long-term safety and efficacy follow-up study (LTF-307) for people who have participated in bluebird bio sponsored clinical studies of lovo-cel.

As of February 17, 2021, a total of 49 patients have been treated with lovo-cel, with up to six years of patient follow-up, in the HGB-205 (n=3), HGB-206 (n=44) and HGB-210 (n=2) clinical studies. The HGB-206 total includes: Group A (n=7), B (n=2) and C (n=35), representing progressive adaptations to the manufacturing and treatment and processes. In the Group C cohort of the Phase 1/2 HGB-206 study, no severe vaso-occlusive events (VOEs) were reported with up to 24 months of follow-up in patients with a history of at least four severe VOEs and at least six months of follow-up.

The safety data profile remains generally consistent with the risks of autologous stem cell transplantation and myeloablative single-agent busulfan conditioning, as well as underlying SCD. One non-serious, Grade 2 adverse event (AE) of febrile neutropenia was considered related to lovo-cel. There were no serious AEs related to lovo-cel.

In the Group C cohort of the HGB-206 study, one patient with underlying cardiopulmonary disease and SCD-related complications died 20 months post-treatment; the treating physician and an independent monitoring committee agreed his death was unlikely related to lovo-cel.

In the initial cohort (Group A) of the HGB-206 study, two patients treated with lovo-cel developed acute myeloid leukemia (AML). After thorough investigations into the cases, bluebird bio determined that these were unlikely related to the insertion of bluebird's lentiviral vector (LVV) gene therapy for SCD.

For more information on lovo-cel studies, visit: https://www.bluebirdbio.com/our-science/clinical-trials or clinicaltrials.gov.

The FDA has granted orphan drug designation, fast track designation, regenerative medicine advanced therapy (RMAT) designation and rare pediatric disease designation for lovo-cel.

lovo-cel is investigational and has not been approved in any geography.

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, β-thalassemia and cerebral adrenoleukodystrophy. 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 longest 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.

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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 financial results, 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 financial results, 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 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 additional patients treated with our product candidates; 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 any one or more of our product candidates will not be successfully developed, approved 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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