FDA Approves First Gene Therapy for Beta-Thalassemia Patients Who Require Regular Red Blood Cell Transfusions: $2.8m Cost

TrialSite Staff

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Aug. 18, 2022, 6:04 p.m.

Gene therapy-focused biotech venture bluebird bio announced recently that the U.S. Food and Drug Administration (FDA) approved ZYNTEGLO® (betibeglogene autotemcel), also known as beti-cel, a one-time gene therapy tailored to treat the underlying genetic cause of beta-thalassemia in adult and pediatric patients who require regular red blood cell (RBC) transfusions. One of the world's most expensive regimens, the price tag will equal $2.8 million for the potentially curative benefit across all ages and genotypes, aiming for the achievement of durable transfusion independence and normal or near normal hemoglobin levels. TrialSite points out a possibly competitive gene therapy product from San Rocco

Therapeutics still in clinical development—and mired in litigation—that would be 4X less expensive and possibly superior, given the purported benefits of an insulator for this class of gene therapy.

As a result of the FDA's action, bluebird bio's CEO Andrew Obenshain shared, "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."

The CEO continued, "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."

A Difficult Condition

This is an important milestone for what is considered 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 United States.

The Approved Product

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.

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

FDA's Priority Review

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.

What's the basis for the approval?

The FDA approval of ZYNTEGLO represents the culmination of nearly a decade of clinical research of gene therapy in patients with transfusion-dependent beta-thalassemia. This gene therapy 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 (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.

Clinical Program Data

Bluebird bio claims it 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 the longest follow-up out to 4 years. Eighty-nine percent (32/36) of the 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.

Safety Issues?

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.

Ongoing Investigations

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.

Limited Access

This now approved product won't be available just anywhere. Due to the complex nature of gene therapy, the bluebird bio gene therapy-based product 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*.

Cost

Price for the treatment alone is a staggering $2.8 million. Undoubtedly, other costs are associated with the several months of activity associated with the treatment, including the provision of medical-related services at the QTCs.

What about Prospective Future Competition?

TrialSite has covered a market competitor still in the clinical trials phase—San Rocco Therapeutics, (SRT) formerly called Errant Gene Therapeutics. This company was the subject of the *TrialSite* piece known as "FamilyMan."

SRT pursues what they position is a superior gene therapy for beta thalassemia and sickle cell anemia.

SRT was founded by Patrick Girondi after the former commodities broker found out his son was diagnosed with thalassemia. The company became the first entity to pass the FDA Recombinant DNA Committee for gene therapy in sickle cell disease and beta thalassemia in 2007. As reported by the Science Advisory Board, they were also the first to get orphan drug designation for thalassemia in the U.S. and Europe as well as cross the finish line with a commercial batch (for 8 to 10 patients) of gene therapy for both sickle cell disease and thalassemia.

Girondi's gene therapy has its roots with the brilliant Michel Sadelain of Memorial Sloan Kettering. SRT has clashed in courts against MSK over access rights and other matters, benefiting bluebird bio along the way.

In "*Family Man*," *TrialSite* exposed how venture capital, academic science, and the pursuit of gargantuan profits interplay with the movement to find novel therapeutics for suffering patients.

In a recent interview on YouTube with *TrialSite's* founder Daniel O'Connor, SRT's CEO Girondi emphasized that the current bluebird bio product ZYNTEGLO lacks an insulator, and that according to experiments conducted by researchers at MSK and other centers, insulators make lentiviral vectors, such as Zynteglo, safer.

Girondi also shared information about his most recent unfortunate setback and legal matter—driven by MSK's withholding of access to the intellectual property needed to finalize clinical development and ultimate commercialization of the SRT gene therapy, which would be priced far more economically. Bluebird bio's ZYNTEGLO is priced 4X that of SRT's planned price point of $700,000, for what Girondi positions would be a superior (and safer) treatment.

Girondi shared with TrialSite in an email that "with a $2.8 million dollar price tag per patient, the approval is a condemnation for the overall patient population and U.S. system of healthcare."

Praises

On the other hand, the Cooley Anemia Foundation went on the record to applaud the approval of ZYNTEGLO for people with beta-thalassemia who require regular blood cell transfusions, shared their National Executive Director Craig Butler. Butler said, "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." He emphasized the exciting prospect

for a one-time curative therapy—potentially life-changing.

Alexis A. Thompson, MD, MPH, Chief of the Division of Hematology, Children's Hospital of Philadelphia went on the record, "Transfusion-dependent beta-thalassemia is associated with an intense treatment burden and significant health risks related to regular red blood transfusions and iron management." Consequently, he continued, "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."

Risk Factors

Note that in bluebird bio's recent press release, notable risk factors are disclosed in association with this newly FDA-approved novel gene therapy, from delayed platelet engraftment and risk of neutrophil engraftment failure to risk of insertional oncogenesis, hypersensitivity reactions and anti-retroviral and hydroxyurea use. Other issues involving adverse reactions, drug interactions, and the like are disclosed.

About bluebird bio, Inc.

Bluebird bio is pursuing curative gene therapies to give patients and their families more 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 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.”

The company’s stock went up slightly thanks to the news. But biotech stock is generally way down in what’s become a pandemic bear market. Although biotech stock boomed early, how matters have changed. Bluebird now trades at 6.78. Its 52-week high/low is **2.87 - 17.8.**

Major holders of its stock include Wellington Management Group LLP, Tang Capital Management, LLC, Blackrock Inc., the Vanguard Group, and Renaissance Technologies, LLC.

FDA Gene Therapy Gene Editing Sickle Hemoglobin

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