

LentiGlobin for Beta Thalassemia: Effectiveness and Value

Revised Background and Scope
February 4, 2020

Background

Beta thalassemia is an inherited blood disorder characterized by reduced or absent synthesis of the beta globin chains of hemoglobin, leading to ineffective erythropoiesis, chronic hemolysis, and significant anemia. It is among the most common monogenic disorders worldwide, with 1.5% of the global population – primarily in the Mediterranean, Africa, the Middle East, and Southeast Asia – carrying a mutation.¹ It is much less common in the United States (US), with an estimated prevalence of 1,000 patients; however, given migration patterns, the prevalence is increasing in the US,² and is likely to continue to increase in the future.

More than 200 disease-causing mutations have been identified in the *HBB* globin gene, which resides on chromosome 11. *HBB* encodes the beta globin proteins that, along with alpha globin proteins, are the building blocks for functional adult hemoglobin. All humans have two copies of the *HBB* gene; each copy produces the beta globin protein. Heterozygotes for the condition carry a mutation in only one *HBB* gene and are generally asymptomatic due to compensation from the other normal gene (beta thalassemia minor or carrier). However, if both *HBB* genes have mutations (homozygotes or compound heterozygotes), there is a reduction (β^+ subtype or beta thalassemia intermedia) or absence (β^0 subtype or beta thalassemia major) of beta globin chains. This imbalance of alpha and beta globin chains results in a lack of production of functional red blood cells.

Severity of beta thalassemia is dependent on several factors, including the number of beta globin chains that are produced, the specific mutation, and any co-inherited mutations (e.g., hemoglobin E). Patients with beta thalassemia major, the most severe subtype due to the complete absence of beta globin chains, typically present in the first six to 24 months of life with severe anemia, failure to thrive, and hepatosplenomegaly.³ Ineffective hematopoiesis leads to expansion of the bone marrow and resultant growth retardation, skeletal changes particularly in the face and long bones of the legs, osteoporosis, leg ulcers, and development of extramedullary masses. High output heart failure from anemia is also common without treatment. Without transfusion therapy, such patients die within the first few years of life, primarily from heart failure or infection.⁴

Patients with beta thalassemia intermedia tend to present later in childhood, typically between the ages of two and six; however, some patients are asymptomatic until adulthood. Such patients also have characteristic deformities of the face and long bones. Common manifestations include osteoporosis, enlargement of the spleen, masses of the spleen, liver, lymph nodes, and spine, leg ulcers, and iron overload secondary to increased intestinal iron absorption.³ Pulmonary hypertension and heart failure are the common cardiac manifestations of beta thalassemia intermedia,⁵ and arrhythmias, heart failure, and cirrhosis may result from the increased intestinal iron absorption. Accumulation of calcium and other minerals may also occur, resulting in pseudoxanthoma elasticum.⁶ Patients may be transfusion dependent or non-transfusion dependent, and this state may fluctuate over time, with transfusions more likely to be needed at times of stress (e.g., pregnancy, infection, surgery).

Patients with beta thalassemia minor are asymptomatic carriers of the disease and have no clinical manifestations other than mild anemia. Identification of such patients is important, however, given the prevalence of genetic mutations, as offspring of two carriers have a 25% risk of having beta thalassemia major.

Note that while the traditional categorization of beta thalassemia relied upon characterization of beta globin chain production, more recently patients have been classified according to their transfusion status (i.e., transfusion dependent beta thalassemia [TDT] or non-transfusion dependent beta thalassemia [NTDT]). For this review, we will focus on TDT patients.

Quality of Life

Although life expectancy has increased with improved treatments, patients with TDT report decreased quality of life, as it affects both physical and mental health.⁷ Women, older patients, and those with more disease complications and side effects from chelation, in particular, reported lower health-related quality of life compared with US norms,⁸ with bone pain being a prominent symptom for older thalassemia patients.⁹ Physical and mental health related quality of life was higher amongst patients with lower iron burden; higher iron burden was associated with lower social functioning.¹⁰ Use of oral iron chelators is also associated with better quality of life,¹¹ provided good adherence to treatment.

Treatments

As treatments for TDT have improved, life expectancy has also increased, and many patients now live into adulthood. Blood transfusion and iron chelation are the standard of care for patients with TDT, with the former suppressing ineffective hematopoiesis and its complications, and the latter treating and preventing complications from iron overload. Indications for transfusion include a hemoglobin < 7 g/dL on two different occasions more than two weeks apart, or a hemoglobin > 7 g/dL with complications such as facial changes, poor growth, fractures, or clinically significant extramedullary hematopoiesis.¹² The goal of treatment is to maintain a hemoglobin level of 9-10.5 g/dL, which has been shown to promote normal growth, suppress bone marrow activity, and minimize iron accumulation.^{13,14} Transfusions may be needed every 2-5 weeks to reach this goal. Some patients, such as those with heart failure, may require higher target hemoglobin levels.¹⁵

Risks of frequent blood transfusions include febrile transfusion reactions, allergic reactions, hemolytic anemia, delayed transfusion reaction, transfusion-related acute lung injury, and transfusion-related graft versus host disease. A significant number of patients with TDT develop alloimmunization, particularly if transfusions start after one to three years of age or after splenectomy,¹⁶ which can result in difficulty finding matched blood and increase the likelihood of delayed transfusion reactions. In low resource countries, the availability and safety of the blood supply is also of concern, with hepatitis B and C infection of particular concern.¹²

The main complication from frequent blood transfusions is iron overload, as the human body lacks a method of excreting excess iron. Accumulation of iron in the body, particularly in the heart, liver, and pituitary gland, can lead to heart failure, cirrhosis, hepatocellular carcinoma, hypothyroidism, hypoparathyroidism, hypogonadism, diabetes, and growth failure. Iron overload is monitored via serum ferritin levels, and more recently, with magnetic resonance imaging of the liver and heart tissues. Lower iron levels are associated with lower rates of cardiac disease and lower mortality.¹⁷

Iron chelation therapy is the main method of both treating and preventing iron overload. The primary goal of chelation is to maintain iron balance in the body by excreting excess iron through urine or feces, and should begin after 10-20 transfusions or when the serum ferritin level rises above 1000 mcg/L.¹² Chelation can also be used as rescue therapy once iron has accumulated, but this is much less efficient and existing damage to tissues may or may not be reversible. There are three iron chelators available: desferrioxamine, which is delivered subcutaneously or intravenously; deferasirox, a once daily oral tablet; and deferiprone, a three times daily oral tablet. Chelation efficiency for these drugs ranges from 7-27% excretion. Deferasirox is the most effective.¹² The main adverse effects from iron chelation therapy include hearing problems, bone growth retardation and local reactions (for subcutaneous or intravenous administration), gastrointestinal symptoms, arthralgia, and neutropenia (for oral chelators). Successful iron chelation has been associated with a decreased risk of hypogonadism and diabetes,^{18,19} and early initiation prior to the age of 10 improves outcomes.¹⁸ Adherence to iron chelation therapy is the main limiting factor of

its success, with higher adherence for patients taking oral therapy.²⁰ Combination chelation therapy may be indicated for severe iron overload, particularly for rescue therapy, and in severe cases, splenectomy may be required.¹²

Hematopoietic stem cell therapy (HSCT) is currently the only curative treatment for TDT. HLA-identical sibling transplant has a cure rate of 80-90% in children;²¹ the success rates in adults is lower, in the 65-70% range.²² The main limiting factor for HSCT is lack of a compatible donor. Fewer than 25% of patients have compatible related or unrelated donors, and transplants with mismatched donors or unrelated umbilical cord blood have a lower success rate.²³ Complications from HSCT include mucositis, infection, graft failure, infertility, and graft versus host disease; there is a 5-10% transplant-related mortality rate.²⁴ If available, HSCT should be offered to patients early in the disease course, prior to the onset of iron overload.¹²

Novel Therapies

Novel approaches to treatment of beta thalassemia include gene therapy and agents to increase gamma globin chain production and offset beta globin chain deficiency (increase in fetal hemoglobin [HbF]), modulate erythropoiesis, and modulate iron metabolism.⁹ Trials of existing drugs such as hydroxyurea, thalidomide, and sirolimus are ongoing, and new agents such as JAK-2 inhibitors and hepcidin mimetics are in development.

Luspatercept-aamt (Reblozyl[®], Acceleron Pharma and Bristol-Myers Squibb/Celgene Corp.) was approved by the US Food and Drug Administration (FDA) on November 8, 2019. Luspatercept is an activin receptor-II trap ligand which inhibits the expression of aberrant cell signaling proteins in erythroid precursors, resulting in improved red blood cell maturation and increased hemoglobin levels.

LentiGlobin (Bluebird Bio), currently marketed in Europe under brand name Zynteglo[®], is an emerging gene therapy that uses a lentivirus vector to insert a functioning version of the *HBB* gene into the patient's own hematopoietic stem cells. This is accomplished via autologous stem cell transplant of engineered cells, leading to an increase in beta globin synthesis and increased hemoglobin levels. LentiGlobin was granted Breakthrough Therapy designation by the US FDA in 2015 and was approved for conditional marketing authorization by the European Medicines Agency in May 2019. A biologics license application for US FDA approval was filed on January 13, 2020 with an anticipated decision in the first half of 2020.

A prior version of this scope included Luspatercept-aamt as a treatment potentially to be considered in this review. After careful consideration, we have decided to concentrate on beta-thalassemia treatments with curative intent. Thus, this review will focus on LentiGlobin.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Patients and patient groups report that although there have been significant improvements in therapy over the years (e.g., the advent of oral iron chelators), transfusion dependency continues to have a significant impact on quality of life. This is not only due to the logistics associated with frequent blood transfusions, but also from complications of the disease or its treatment and the stress associated with managing a lifelong chronic disease. Additionally, patients may have difficulty accessing beta thalassemia specialists for treatment, including a lack of local providers with expertise in treating the disease and challenges in obtaining insurance coverage for office visits. Patients on Medicaid face particular difficulty getting treatment from a thalassemia specialist due to limitations on out-of-state coverage. Insurance coverage of iron chelation therapy was also mentioned as an obstacle, with prior authorization often required. Patients and patient groups are interested and optimistic about the potential for cure using gene therapy treatments such as LentiGlobin, though they are concerned about its cost and durability of its effect. Additionally, some patients expressed reluctance to use such novel therapies due to the need for myeloablative therapy, uncertainty of efficacy, and potential long-term side effects.

In response to comments we received on the draft scope, we have restricted our patient population to patients 12 and older who are eligible for stem cell transplant but lack a compatible donor to be consistent with the clinical trial population and the expected labeling for LentiGlobin. Additionally, we have removed HSCT therapy as a comparator, since for the majority of patients eligible for LentiGlobin therapy, HSCT is not a viable treatment option. Although we appreciate the comments suggesting inclusion of luspatercept-aamt in our review, we have elected not to include luspatercept-aamt either as an intervention or a comparator due to our focus on therapies with curative intent and the lack of clarity about the current role of luspatercept-aamt in the treatment pathway for beta thalassemia patients. We have also removed venous thromboembolism as a key outcome, as this outcome was mainly relevant to luspatercept-aamt. Finally, we have noted that insurance coverage of iron chelation therapy is a challenge for patients.

Report Aim

This project will evaluate the health and economic outcomes of LentiGlobin for patients living with TDT. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

We propose to assess LentiGlobin under an adaptation of the ICER value framework for treatments of high-impact “single and short-term therapies” (SSTs), defined as therapies that are delivered through a single intervention or a short-term course (less than one year) of treatment that offer a significant potential for substantial and sustained health benefits extending throughout patients’ lifetimes. SSTs include two subcategories: potential cures that can eradicate a disease or condition, and high-impact therapies that can produce sustained major health gains or halt the progression of significant illnesses. Further details of ICER’s value framework adaptation for SSTs can be found [here](#). Following formal public comment and discussions with stakeholders, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

Scope of Clinical Evidence Review

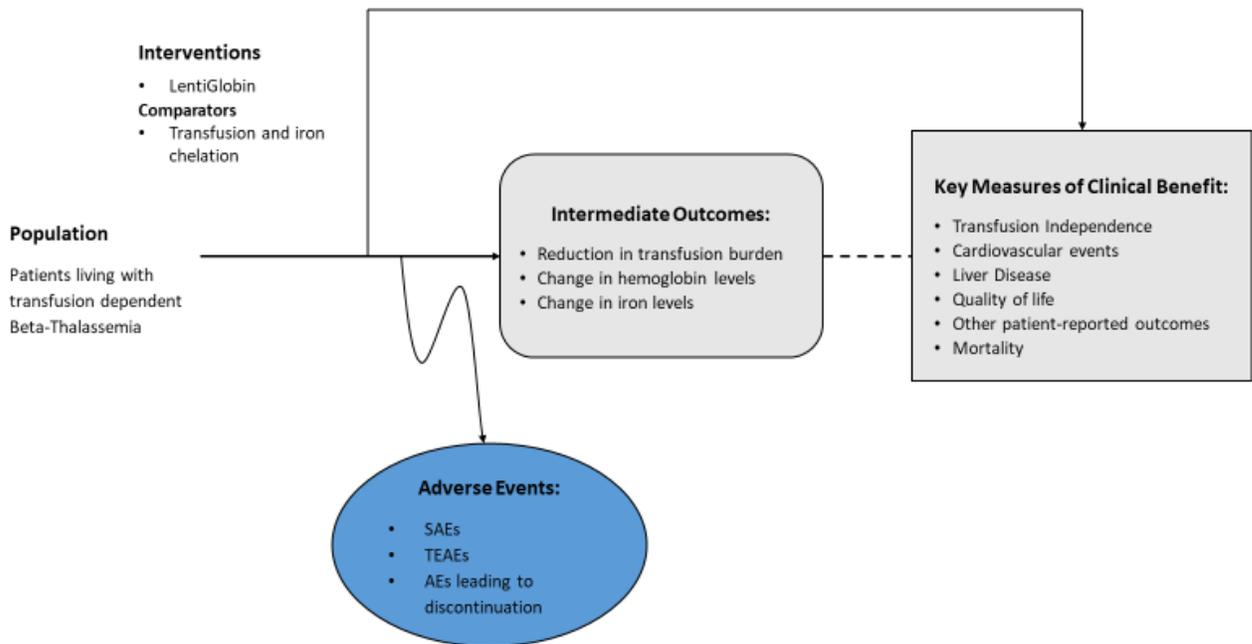
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews. High-quality comparative cohort studies will be considered, particularly for comparisons, measures, uncommon adverse events, and time horizons that have not been featured in randomized trials. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature containing evidence that meets ICER standards (for more information, see <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/>).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework (<https://osf.io/7awvd/>).

Analytic Framework

The general analytic framework for assessment of gene therapy for TDT is depicted in Figure 1.1 below.

Figure 1.1. Analytic Framework



AE: adverse event, SAE: serious adverse event, TEAE: treatment emergent adverse event

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., reduction in transfusion burden), and those within the squared-off boxes are key measures of benefit (e.g., quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.²⁵

Populations

The population of focus for the review is children and adults twelve years and older living with TDT who are eligible for stem cell transplant and do not have access to a matched donor.

Data permitting, we intend to assess evidence on treatment for TDT for the following sub-groups:

- non- β^0/β^0 genotype
- β^0/β^0 genotype

Interventions

The intervention of interest for this review is LentiGlobin gene therapy (Bluebird Bio).

Comparators

Data permitting, we intend to compare the intervention to the standard clinical management, including blood transfusions and iron chelation.

Outcomes

The key outcomes and harms of interest from the clinical trials are listed below.

Key Outcomes and Harms

- Transfusion independence
- Reduction in transfusion burden
- Change in hemoglobin levels
- Change in iron levels (including serum ferritin, liver iron concentration, and myocardial iron deposition)
- Engraftment or neutrophil count
- Pulmonary hypertension
- Cardiovascular events (e.g., arrhythmia and congestive heart failure)
- Liver disease
- Bone pain
- Quality of life
- Other patient reported outcomes
- Mortality
- Serious adverse effects (SAEs)
- Treatment emergent adverse effects (TEAEs)
- Adverse events (AEs) leading to discontinuation

Timing

Evidence on intervention effectiveness will be derived from studies of any duration that meet the study design criteria set forth above and measure the outcomes of interest.

Settings

All relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the Table 1.1 below.

Table 1.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to “the comparator,” there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a *de novo* Markov model to assess the lifetime cost effectiveness of LentiGlobin as compared to standard clinical management, including blood transfusions and iron chelating agents. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses and

other indirect costs will be considered in a separate scenario analysis. The modeled population will consist of children and adults twelve years and older living with TDT who are eligible for hematopoietic stem cell transplantation but do not have access to a matched donor. We intend to model the following sub-groups, as data allow: non- β^0/β^0 genotype and β^0/β^0 genotype.

A detailed economic model analysis plan with proposed methodology, model structure, parameters, and assumptions is forthcoming. The model structure will be based in part on a literature review of prior published models of TDT.^{26,27} The model will consist of health states including transfusion dependent, transfusion reduction, transfusion independent, and dead. Health states will differ based on hemoglobin levels, iron levels, and frequency of transfusions. Utility, mortality, and cost for each health state will be estimated using time-varying relationships that are a function of hemoglobin level, iron level, and/or transfusion frequency history. A cohort of patients will transition between health states during predetermined cycles of one year over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost effectiveness may be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and the associated direct medical costs and utility assigned to each health state. The health outcome of each intervention will be evaluated in terms of the number of transfusions, life-years, equal value life years gained (evLYG), and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to treatment acquisition, administration and monitoring, condition-related care, and serious adverse events. In addition, productivity impacts and other indirect costs associated with beta thalassemia, transfusion dependence, and treatments will be included in a separate analysis as data allow. All future costs and outcomes will be discounted 3% per year. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per transfusion avoided.

Uncertainty will be assessed through one-way and probabilistic sensitivity analyses. A number of scenario analyses will also be conducted, including incorporating indirect costs such as patient and caregiver time and productivity losses in a separate societal analysis. Results will be presented in aggregate and separately for stated sub-groups as data allow.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the cost-effectiveness model for treatment costs and cost offsets. This potential budgetary impact analysis will indicate the relation

between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: <http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf>.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see <https://icer-review.org/material/final-vaf-2017-2019/>). These services are ones that would not be directly affected by treatment with LentiGlobin (e.g., reduction in blood transfusion burden, hospitalizations, etc.), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of TDT beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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