Betibeglogene Autotemcel for Beta Thalassemia

Revised Background and Scope

December 23, 2021

Background

Beta thalassemia is an inherited blood disorder caused by a genetic mutation of the *HBB* gene that leads to reduced or absent synthesis of the β-globin proteins of hemoglobin, components of red blood cells responsible for carrying oxygen. When β-globin is markedly reduced or absent, it leads to ineffective production and increased destruction of red blood cells, manifesting in clinically significant anemia.

Beta thalassemia is an autosomal recessive disorder. Individuals that carry a mutation in only one copy of the *HBB* gene are generally asymptomatic or only have a mild anemia (beta thalassemia minor or trait, Hb>10.0 g/dL). However, if both copies of the *HBB* gene have a mutation, there will be a reduction or absence of β-globin. The degree to which β-globin is reduced depends on the specific mutation and how many genes are affected: β0/β0 (completely absent β-globin), β+/β+ (some β-globin production, severity depends on mutation), or β+/β0 (one gene copy produces some β-globin, the other produces none). It is estimated that 1.5% of the global population carries at least one defective copy of the *HBB* gene, with certain geographic areas having a higher local prevalence – primarily in the Mediterranean, Africa, the Middle East, and South Asia.[1-3] Patients with completely absent β-globin have a more severe clinical course, typically presenting in the first six to 24 months of life with severe anemia, failure to thrive, and end organ damage; prompt initiation of transfusion therapy is required to prevent early mortality.[4,5] Conversely, patients with some β-globin production have variable clinical presentations with some patients depending on routine transfusions to maintain health and quality of life, while others might have mild symptoms or only receive transfusions in times of stress (e.g., pregnancy, infection, surgery). Historically, patients with absent β-globin (β0) were considered to have thalassemia major and those with reduced β-globin (β+) were considered to have thalassemia intermedia. The 2021 Guidelines published by the Thalassaemia International Federation (TIF) classify beta thalassemia phenotypically into two main groups based on clinical severity and transfusion requirement regardless of the underlying genotype: transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT).[5]

Lifelong, regular blood transfusions and removal of excess iron through chelation are the mainstays of treatment for patients with TDT. Routine transfusions, typically every two to five weeks, aim to keep hemoglobin at a level that suppresses the body's production of its own (abnormal) hemoglobin. However, excess iron accumulates as a consequence of repeated transfusion; chelation is critical for treating and preventing complications from iron overload (e.g., pulmonary hypertension, liver dysfunction, cardiac manifestations), the main source of morbidity and mortality in TDT. In addition, patients with TDT also contend with other disease-related complications such as problems with growth and development, diabetes and other endocrine abnormalities, and fertility and pregnancy-related concerns. There is also the ongoing risk of transfusion-related side effects and infections, although the latter are rare with modern blood screening procedures. Standard of care may also include treatment with luspatercept-aamt (Reblozyl®, Acceleron Pharma Inc. and Bristol Myers Squibb/Celgene Corp.), a biologic that can increase red blood cell production thereby reducing transfusion burden in some patients.

Hematopoietic stem cell therapy (HSCT) is currently the only curative treatment for TDT. Ideally, HSCT is performed in children younger than 14 years of age with a human leukocyte antigen (HLA)-matched sibling donor. In such candidates, the cure rate is over 90% with a 4% risk of mortality. The cure rate decreases in older patients, those with extensive iron toxicity, and those without a matched donor.[6] Lack of compatible donors is a central limitation of initiating HSCT as fewer than 25% of patients have compatible related or unrelated donors.[7]

Betibeglogene autotemcel ("beti-cel", bluebird bio), previously marketed in Europe under the brand name Zynteglo™, is an emerging curative gene therapy for beta thalassemia. Beti-cel works by using a modified virus (lentivirus vector) to insert a functioning version of the *HBB* gene into the patient's own blood cells. This is accomplished by retrieving stem cells from the patient's own blood, engineering them outside of the body, and then transplanting the corrected cells with functioning *HBB* back into the body. The person must receive chemotherapy to prepare the bone marrow to receive the corrected cells and to produce new red cells with normal β-globin/hemoglobin, but regimen of chemotherapy is generally less intense than in HSCT. The FDA accepted bluebird bio's Biologics License Application (BLA) of beti-cel for priority review on November 22, 2021, and the PDUFA date is set for May 20, 2022.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and patient advocacy groups, clinicians, payers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public as well as input that occurred during an earlier planned ICER report on beti-cel in 2019. Two patient advocacy groups, the Thalassaemia International Federation (TIF) and the Cooley's Anemia Foundation, and the manufacturer provided

comment on a draft version of this scope during the three-week public comment period. Based on feedback received, revisions to this document were made. Our scope was revised to clarify nomenclature and to expand our overview of the complications of thalassemia. We have also amended our approach to the serious and ultra-rare conditions framework. 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.

Although life expectancy has increased with improved treatments, patients with TDT still report decreased quality of life due to the impact on physical and mental health.[8,9] We heard from patients and clinicians that living with severe forms of beta thalassemia requires being tethered to the health care system and often to a geographic area with a medical center that can provide thalassemia care. Management of the condition has been described as a part-time job for both patients and their caregivers. Patients plan their lives around transfusions, which can disrupt their ability to travel, take vacations, work, and study. Some patients receive transfusions as often as every two weeks, in addition to regular MRI and DEXA imaging, monitoring of laboratory values, and visits to clinical specialists (e.g., endocrinologists). Regular transfusions and blood draws can be technically challenging in young children, causing stress in patients and caregivers. Some patients require semi-permanent catheters (i.e., ports) to facilitate regular transfusions and blood draws, which carry a risk of infection. Patients and their caregivers also spend hours calling doctors' offices, navigating insurance policies, and managing other administrative aspects of their condition. Patients and caregivers also emphasized how quality of life is markedly impacted by other manifestations of thalassemia (e.g., diabetes, problems with growth or development). Infertility was highlighted as a particular concern.

Women, older patients, and those with more disease complications or side effects from management of iron overload (i.e., chelation therapy), on average, report lower health-related quality of life compared with US population norms.[10] Adherence to iron chelation is associated with better quality of life, although patients who suspend chelation therapy feel "normal" for a few weeks or months.[11] The lack of immediate symptomatic decline, route of administration and dosing, as well as the side effects of chelation therapy can make adherence a challenge.

We received feedback from TIF that in a recent report by TIF, the majority of survey respondents with thalassemia demonstrated a positive attitude towards gene therapy with a significant proportion interested in gene therapy for themselves or children. Despite enthusiasm toward the possibility of curing beta thalassemia, patients whose condition is well-managed with current standard of care may be reluctant to modify their treatment regimen. There is cautious optimism about the promise of gene therapy, and we heard from patients that they will carefully weigh costs, insurance coverage, duration of clinical benefit, and risks once it becomes available.

Report Aim

This project will evaluate the health and economic outcomes of beti-cel for beta thalassemia. 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.

Applicable Framework Adaptations

We will assess beti-cel under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs) and under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions.

In accordance with the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs), beti-cel meets the following criteria:

- The therapy is delivered through a single intervention or a short-term course (less than one year) of treatment that offers a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes.
- The therapy can eradicate a disease or condition, or produce sustained major health gains that can halt the progression of significant illnesses.

In the Draft Scope, we did not plan to assess beti-cel under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions because a similar treatment is currently being studied within adult and pediatric patients with sickle cell disease (approximately 100,000 Americans have sickle cell disease).[12,13] Following clarification from the manufacturer that a separate gene therapy product, lovotibeglogene autotemcel ('lovo-cel'), will be marketed and priced for the treatment of sickle cell disease, ICER now plans to review beti-cel in accordance with the ICER Value Framework for treatments of serious, ultra-rare conditions given that the following criteria are met:

- The eligible patient population for the treatment indication included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals. The treatment offers a major gain in improved quality of life and/or length of life.

As noted in the ICER Value Framework, when a treatment is deemed to qualify as both SST and for an ultra-rare disease, all elements of both methods adaptations will be pursued.

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 long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Data permitting, we will 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 revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is patients living with TDT, typically defined as eight or more transfusions per year. While the historical categorization of beta thalassemia relied upon characterization of β-globin chain production and genotyping, more recently patients have been characterized according to their transfusion status (i.e., TDT or NTDT) as this is most closely aligned with clinical outcomes and quality of life. We will consider both adult and pediatric patients with TDT without pre-specified age limits, however patients must be clinically eligible to undergo bone marrow conditioning.

Data permitting, we intend to assess evidence on treatment for TDT for groups stratified by:

- Age
- Genotype (β0/β0 and non-β0/β0)

Interventions

The intervention of interest for this review is betibeglogene autotemcel ("beti-cel", bluebird bio) gene therapy.

Comparators

We intend to compare the intervention to standard clinical management, including blood transfusions and iron chelation. Data permitting, we will also compare the intervention to HSCT in transplant eligible patients.

Outcomes

Key Outcomes and Harms

- Patient-Important Outcomes
    - Transfusion independence
    - Reduction in transfusion burden
    - Manifestations of iron overload:
        - Cardiovascular events
        - Liver disease
        - Splenomegaly and splenectomy
        - Endocrine disease
    - Bone pain
    - Health-related quality of life
    - Other patient reported outcomes
    - Fertility
    - Mortality
    - Growth abnormalities
    - Burden of care for patients and caregivers (e.g., missed time from work)
    - Transplantation success/engraftment (e.g., neutrophil count)
    - Serious adverse effects (SAEs)
    - Treatment emergent adverse effects (TEAEs)
    - Adverse events (AEs) leading to discontinuation

- Other Outcomes
    - Hemoglobin levels
    - Iron levels (including serum ferritin, liver iron concentration, and myocardial iron deposition)
    - Health care resource utilization

Timing

Evidence on intervention effectiveness and evidence on harms 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 general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant): Beti-cel could have a significant impact on the entire "infrastructure" of care around beta thalassemia, including but not limited to pre-conception planning, searching for matched donors, and monitoring of affected individuals. It may also change how patients are cared for in ways that extend beyond the treatment itself and this framework may extend to to the use of gene therapy for other conditions.

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a *de novo* cohort-level decision-analytic model to assess the lifetime cost effectiveness of beti-cel relative to treatment with blood transfusions plus iron chelating agents. The model structure will be based in part on a literature

review of prior published models of beta thalassemia. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained.

The primary population for the economic assessment will be consistent with beti-cel trial populations (patients living with TDT and must be clinically eligible to undergo bone marrow conditioning). We intend to model the following sub-groups, as data allow: non-β0/β0 genotype, β0/β0 genotype, and by age. The model will consist of health states including transfusion dependent, transfusion independent, and dead. An intermediate "transfusion reduction" health state may also be considered if evidence supports such an added health state for either a modeled intervention or comparator. A cohort of patients will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost effectiveness will 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. Treatment effectiveness will be estimated through methods detailed in the clinical evidence review protocol and model analysis plan.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, AEs, and direct medical costs. The health outcome of each intervention will be evaluated in terms of number of transfusions, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years (evLYs) 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 drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in the societal analysis as data allow. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per transfusion avoided.

In separate analyses, we will explore the potential health care 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 economic model for treatment costs and cost offsets. This 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 here.

Identification of Low-Value Services

ICER includes 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 ICER's Value Assessment Framework). These services are ones that would not be directly affected by beti-cel, such as administration of blood transfusions, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of beta thalassemia 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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