

THEMES AND RECOMMENDATIONS

	betibeglogene autotemcel (beti-cel, bluebird bio)
Evidence Rating	B+: the evidence demonstrates that beti-cel is superior overall to the current standard of care, but the magnitude of that overall net health benefit is less certain, ranging from incremental to substantial
Estimated Annual Price	Placeholder price: \$2.1 M
Change from Annual Price Required to Reach Threshold Price	N/A due to placeholder price

“Beta-thalassemia is a serious blood disorder, and while treatment has improved, patients with transfusion-dependent-thalassemia (TDT) still have decreased life expectancy and burdensome care that impacts all aspects of their lives. Previously, a minority of patients had access to curative allogeneic bone marrow transplant; beti-cel provides an additional potentially curative option for many patients with TDT. New potentially curative therapies for beta-thalassemia bring the promise of considerable lifetime benefit, but there also remains substantial uncertainty regarding longer-term safety and the durability of benefits. Beti-cel is cost-effective at a high price in part because it offsets current very high costs of care; a somewhat lower price would be needed if half of those offsets were returned to the medical system.” – **ICER’s Chief Medical Officer, David Rind, MD**

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility to facilitate meaningful patient access to curative therapies for beta thalassemia in ways that do not exacerbate disparities.
- New potentially curative therapies for beta-thalassemia bring the promise of considerable lifetime benefit, but there also remains substantial uncertainty regarding longer-term safety and the durability of benefits. In the context of this heightened uncertainty, manufacturers should seek to base access on outcomes-based payment agreements with all payers.
- Manufacturers should align prices with independent estimates of the patient-centered therapeutic value of their treatments. In the context of high-impact single or short-term therapies, transparent consideration should be given to a pricing scenario that “shares” any substantial cost-offset of treatment so that potentially large cost-offsets are not used to justify exceedingly high one-time prices.
- Payers should use the FDA label as the guide to coverage policy without seeking to unduly narrow coverage using clinical trial eligibility criteria. Payers should also engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time (e.g., fertility preservation).

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Beta-thalassemia is a rare blood disorder with the potential for high morbidity and mortality when treated suboptimally. Transfusion-dependent thalassemia (TDT), the most severe form of this disease, is managed through lifelong regular blood transfusions and iron chelation therapy to avert the consequences of iron overload. There are likely between 1,000 – 1,500 people in the US living with TDT, but there are estimated to be about 1.25 million carriers of the genetic defect that is responsible for thalassemia. Until recently, the only curative option for TDT was allogeneic hematopoietic (blood) stem cell transplantation (HSCT) from a matched donor, ideally a sibling. HSCT requires high doses of conditioning chemotherapy and places the recipient at risk of complications associated with HSCT itself (e.g., graft vs. host disease) and finding an HSCT match is difficult as fewer than 25% of patients have access to a suitable match.

Life expectancy still lags far behind population norms even with improved treatments: from 2011 to 2021 the median age of death for a person in the US with TDT was 37. Additionally, patients with TDT still report decreased quality of life due to the impact on physical and mental health. Patients and clinicians reported to us that living with severe forms of beta thalassemia requires being “tethered to the health care system” and often to a specific region near a medical center that can provide thalassemia care. Some patients receive transfusions as often as every two weeks, and nearly all patients plan their lives around transfusions. Regular transfusions and chelation can be technically challenging in young children, causing stress in patients and caregivers.

Betibeglogene autotemcel (beti-cel), manufactured by bluebird bio, is a gene therapy that provides an additional potentially curative option for patients with TDT. Beti-cel is manufactured *ex vivo* utilizing an individual’s own hematopoietic stem cells (HSCs). A

lentiviral vector (BB305) is then used to add functional copies of the β -globin gene (β^{A-T87Q}) to patients’ HSCs. The modified HSCs (beti-cel) are then infused intravenously back into the individual following conditioning chemotherapy. The Food and Drug Administration (FDA) accepted bluebird bio’s Biologics License Application (BLA) of beti-cel for priority review on November 22, 2021, and the revised PDUFA date is set for August 19, 2022. Public statements made by the manufacturer suggest that beti-cel pricing will be consistent with an outcome-based payment plan of five equal yearly payments totaling \$2.1 million for individuals who achieve and maintain transfusion independence.

The systematic review yielded five studies of beti-cel: two Phase I/II trials, two Phase III trials, and one long-term follow-up cohort study of trial participants. Each of the four trials were open-label single arm designs. A manufacturing change occurred between the Phase I/II and Phase III trials; therefore, we gave greater emphasis to the results from the Phase III trials.

Transfusion independence in the Phase III trials was achieved in 90% of the patients who received beti-cel. Transfusion independence was sustained over a median length of follow-up of 42 months (range 23-88). However, this duration is not long enough to remove uncertainty regarding the durability of effect over a longer time period. Because of the uncertainty about these risks and the durability of the clinical benefit, we judge that the evidence demonstrates that beti-cel is superior overall to the current standard of care, but the magnitude of that overall net health benefit is less certain, ranging from incremental to substantial (“B+”).

Clinical Analyses

Table 1. Evidence Ratings

Treatment	Comparator	Evidence Rating
betibeglogene autoemcel	Standard of Care	B+

Economic Analyses

LONG-TERM COST EFFECTIVENESS

The manufacturer has suggested publicly that beti-cel will be priced based on its clinical value to patients only, rather than its ability to offset costs of current therapy. ICER's single and short-term therapy (SST) value assessment framework includes a scenario analysis where half the cost offsets from an SST are returned to society rather than all being credited to the price of the treatment. While in the base case, no discount is needed from the anticipated price of \$2.1 million to achieve typical ICER Health Benefit Price Benchmarks (HBPBs), assuming 50/50 shared savings, the HBPB range is \$1.3 to \$1.8 million.

In summary, despite remaining uncertainties, the evidence suggests that beti-cel provides net health benefits to patients with TDT. Given the high annual costs of standard care, cost-effectiveness modeling finds that this new treatment meets commonly accepted value thresholds at an anticipated price of \$2.1 million with an 80% payback option for patients who do not achieve and maintain transfusion independence over a five-year period. However, if half of the lifetime cost savings from the therapy are returned to society, then discounts between 15% and 38% off the anticipated price are required to meet commonly accepted thresholds.

Economic Analyses

POTENTIAL BUDGET IMPACT

Results showed that at the anticipated price of \$2.1 million per treatment course (to be paid upfront but including an 80% payback option if patients do not achieve transfusion independence), all eligible patients could be treated over the span of five years without crossing the ICER budget impact threshold of \$734 million per year. Similarly, all eligible patients could be treated with beti-cel without reaching the potential

budget impact threshold at the three threshold prices (approximately \$1.85 million, \$2.12 million, and \$2.40 million per course of treatment).

ICER is not issuing an Access and Affordability Alert for beti-cel given that all patients eligible for treatment can be treated without crossing the ICER potential budget impact threshold.

Public Meeting Deliberations

VOTING RESULTS

- All panelists (12-0) found the evidence is **adequate** to demonstrate a net health benefit when beti-cel is compared to standard clinical management.
- A majority (9-3) of panelists found that beti-cel represents “high” long-term value for money.

During their deliberations, panel members also weighed the therapy’s other potential benefits, disadvantages, and contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

For any patient with TDT:

- Magnitude of the lifetime impact of TDT on individuals.

The implications of treatment with beti-cel on:

- 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;
- A potential advantage for therapies that offer a new treatment choice with a different balance or timing of risks and benefits that may be valued by patients with different risk preferences.

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public

hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)) and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).