PATIENTS RISING NOW

Guide for Commenting on ICER's Draft Evidence Report on Treatments for Beta Thalassemia

On April 13, 2022, ICER released its draft evidence report, "Betibeglogene Autotemcel for Beta Thalassemia." This document provides a framework for considering what aspects of betibeglogene autotemcel (beti-cel) – a potential curative new gene therapy for beta thalassemia – are important to patients and their families, and how to consider presenting those perspectives. This guide specifically provides insights about how to read and respond to ICER's draft evidence report, as well as how to request a slot to make comments during ICER's public meeting.

Key Dates

April 13, 2022:	Draft Evidence Report released
May 10, 2022:	Written comments due by 5:00pm ET; deadline to submit request to speak at Public Meeting
June 2, 2022:	Updated Evidence Report released
June 17, 2022:	Public Meeting conducted by ICER's New England Comparative Effectiveness Public Advisory Council (CEPAC)
July 19, 2022:	Final Evidence Report and Public Meeting Summary released

Background & How to Participate

The Institute for Clinical and Economic Review (ICER) is a private entity that uses its own analytical process and "value framework" to assess potential new treatments for a variety of diseases. Those assessments often occur before FDA approval, and may result in conclusions that could harm patients by limiting access to new and innovative treatments. You can learn more about ICER here.

There are two primary ways advocates and other stakeholders can give input:

1. **Submit written comments on the draft report, which are due to ICER by 5:00pm ET on May 10.**
2. **Request a slot to make oral comments during ICER's June 17 meeting.**

Submitting written comments on the draft report

Written comments must be submitted to publiccomments@icer.org as a Word document in 12-point Times New Roman font, and are limited to 5 pages, not including references or appendices. The deadline to submit written comments is 5:00pm ET on May 10, 2022.

Requesting a slot to make oral comments

ICER's public meeting on its revised report and discussion by one of its advisory committees is scheduled for June 17, and will be held virtually. You can register to watch the meeting here. ICER's meetings have a short period available for public comments. To make a request to speak, send an email to publiccomments@icer.org with the person's name, title, and organization. The deadline to make a request to speak is 5:00pm ET on May 10, 2022. Oral comments are limited to no more than five minutes per speaker.

NOTE: Not all requests to make public comments are granted. According to ICER: "We sort through all the requests to make an oral public comment at the meeting. Because we only have a limited time for oral comments at the public meeting, we can only allow a few stakeholders to share their perspective."

Key Points to Consider for Written or Oral Comments

Clinical Effectiveness

- Beta thalassemia is a disease caused by a genetic mutation that results in the person's blood cells containing hemoglobin molecules that are unable to effectively carry oxygen. Children who have two faulty hemoglobin genes fail to thrive, and this severe form of beta thalassemia usually presents between ages 6 months to 2 years old, with the child then starting treatment with transfusions every few weeks. Although transfusions are effective in addressing the faulty hemoglobin genes, they also cause iron levels to build up in the patient, which requires an additional treatment called chelation to remove the excess iron. More recently, blood stem cell transplants – generally from an appropriately genetically matched sibling – have been used when possible.

- The current ICER review of treatments for transfusion-dependent beta thalassemia is focused on betibeglogene autotemcel (beti-cel), a gene therapy treatment that is still undergoing FDA review. The FDA is expected to make a decision on or before August 19, 2022.

- Beti-cel is a potential cure for transfusion-dependent beta thalassemia. It works by inserting a gene for the normal functioning hemoglobin molecule into the patient's own blood stem cells, which have first been removed from the person. Those modified stem cells are then infused back into the person where they seed the bone marrow, enabling the person to make their own blood cells carrying normal hemoglobin.

- ICER's draft evidence report relied on data from five different trials of beti-cel. Because transfusion-dependent beta thalassemia is a rare disease, the data from these trials was from a very limited number of people (22 people in the two phase I/II trials, 41 people in the two phase III trials, and 35 people in a long-term follow-up trial of individuals from the other four studies). Because of the nature of the beti-cel treatment, there was no control or placebo group. Fortunately and perhaps surprisingly, despite the studies' inherent methodological limitation, ICER did not discount the data. As expected, the trial data showed dramatic curative benefits; 89% of people who received the beti-cel treatment no longer required transfusions. And, over the average follow-up period of 42 months, none of that 89% reverted to requiring transfusions.

- The primary side effect of the treatment was from the bone marrow suppressive treatments that the people required prior to receiving their own modified blood stem cells. The most common adverse effect was mouth sores, but none of the people in the clinical trials died, and more serious side effects were uncommon. As ICER summarized, "Beti-cel infusion is associated with mild side effects, but few patients experienced serious adverse events, and no deaths were reported." However, given the small number of people involved in the trials, very serious rare side effects could not be ruled out.

- ICER's review also notes the significant burden on families and patients with transfusion-dependent thalassemia. Two specific burdens cited were the time required to obtain transfusions every few weeks (almost 700 hours per year per patient), and the feeling of being "tethered" to the health care system so that patients were limited in their ability to travel or where they could live. Overall, managing beta thalassemia was time-consuming enough that it was viewed by individuals and their family members as a "part-time job."

- Given beti-cel's dramatic clinical benefits, (e.g., eliminating the need for frequent transfusions and medical visits with a low rate of serious side effects), it is not

surprising that the people in the clinical trials also reported improvements in quality of life using several standard measures. For example, the draft report's summary of this data includes, "pediatric and adolescent patients experienced a mean improvement of 10 points [on the PedsQL scale] 24 months after receiving beti-cel, which exceeded the minimally clinically important difference (MCID) of 4.36."

- In doing its evaluation of beti-cel, ICER concluded that people who have an appropriately genetically matched sibling would be more likely to get a donor blood stem cell transplant, rather than beti-cel. Therefore, ICER only compared beti-cel with standard transfusions and related treatments for individuals who do not have the option of a sibling matched blood stem cell donor.

Recommendation: Advocates for better treatments for people with beta thalassemia – and their families – should consider making the following points in their written or oral comments:

- Advocates should highlight that beti-cel has been found to provide dramatic, curative clinical benefits, and is clearly superior to "standard of care" with ongoing transfusions. And compared to sibling stem cell transplant, it does not require ongoing treatment with immunosuppressive medicines, which the COVID pandemic has demonstrated presents potential serious ongoing challenges for proper immunization and risk of infections.

- Provide your personal perspectives and insights about beta thalassemia – as someone who has the condition yourself, or a friend or family member of a patient with this disease. Describe your insights about the importance of having such a curative treatment, and what that means for quality of life for the person with transfusion-dependent beta thalassemia (including their education and work choices), as well as for their family and friends.

- While beti-cel will not be appropriate for every person with beta thalassemia (i.e., it is being developed and intended only for individuals dependent on frequent transfusions), since this is one of the first gene therapy treatments that has been shown to be safe and effective, it is potentially an important overall step in curing many other inborn genetic conditions. Therefore, comments about the importance of such an initial step for people with a wide variety of genetic conditions would also be appropriate.

Cost Effectiveness

- Of note, this gene therapy treatment was approved in Europe in May 2019 with the name Zynteglo™. However, because of reimbursement challenges from government health programs, very few patients were actually able to receive the treatment, and in mid-2021 the company started withdrawing it from the European market. Other than continued follow-up with people who had been in clinical trials, all activities in Europe for Zynteglo™ ceased in early 2022.

- ICER's economic modeling and analysis has at its core the concept of Quality Adjusted Life Years (QALYs). The use of QALYs for making decisions about payment, coverage, and rationing of care has been widely criticized because QALY assumes that people with less-than-perfect health have diminished quality of life, so QALYs discriminate against people with chronic conditions and disabilities.

- Because of the clear and significant clinical benefits – not the least of which is beti-cel's ability to eliminate patients' need for very frequent and expensive transfusions and associated treatments – ICER found beti-cel to be cost-effective for both the healthcare system and society at large. Specifically, ICER found that with an estimated price of $2.1 million per person (with payments spread out over five years), beti-cel costs-per-QALY gained were $92,200 for the healthcare system, and $33,600 when the scope was expanded to include greater society benefits. Both of those numbers are below ICER's middle-range threshold of $100,000/QALY, and the significantly lower amount for the "Modified Societal Perspective" reflects the very significant costs and burden beta thalassemia currently places on people, their families and society overall. (See Table ES2 below.)

Table ES2. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD Year Averted
Health Care System Perspective					
Beti-cel	SOC	$92,200	$89,500	$167,600	$24,700
Modified Societal Perspective					
Beti-cel	SOC	$33,600	$33,300	$61,300	$9,000

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

- ICER summarized that conclusion in the draft report: "[t]he cost-effectiveness findings were driven by the lifetime opportunity to reduce chelation and transfusion costs (and reduce productivity costs in the modified societal perspective) while also demonstrating health gains that may be considered meaningful to those living (or

caring for those living) with [Transfusion-Dependent Thalassemia]." ICER quantified that finding in the table below, and stated, "Beti-cel transplant incurred additional costs but resulted in fewer transfusion-dependent years and more QALYs [and] life years…."

Table E3.1. Undiscounted Results for Beti-cel Compared to SOC

Treatment	Treatment Cost*	Transfusion and Chelation Costs†	Total Cost	TD Years	QALYs	Life Years	evLYs
Health Care System Perspective							
Beti-cel	$1,890,000	$430,000	$3,320,000	5.98	39.02	49.02	39.61
SOC	-	$3,250,000	$4,060,000	38.36	25.41	38.36	25.41
Modified Societal Perspective							
Beti-cel	$1,890,000	$430,000	$3,550,000	7.26	38.93	49.02	39.53
SOC	-	$3,250,000	$4,850,000	38.36	25.29	38.36	25.29

evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care, TD: transfusion dependent

* Only includes beti-cel acquisition cost (i.e., excludes workup, preparation, transplant, post-transplant monitoring and normalization period costs).

† Only includes transfusion costs and chelation acquisition costs (i.e., excludes chelation administration and monitoring costs)

- Another scenario ICER modeled in its draft report used the characteristics of the clinical trial population in its analysis, and found that beti-cel was both more effective and less costly than standard care. (See Table E5.2 below)

Table E5.2. Scenario Analysis Results using Phase III Baseline Patient Characteristics

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD Year Averted
Health Care System Perspective					
Beti-cel	SOC	$60,600	$59,000	$123,600	$15,700
Modified Societal Perspective					
Beti-cel	SOC	Less costly, more effective	Less costly, more effective	Less costly, more effective	Less costly, more effective

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

- One of the more controversial aspects of ICER's reports about potential new treatments is their "potential budget impact" section, which assumes the U.S. healthcare system is a monolithic single payer entity. ICER's budget impact process asserts that in any year, all new medicines should not receive more than a certain amount of money in total – regardless of how much they benefit patients. That dollar amount is based upon the average total spending on medicines in prior years divided by the average number of new treatments the FDA had approved in recent

years – which is then increased by U.S. GDP +1.0% per year. Interestingly, because there are so few people in the U.S. with transfusion-dependent beta thalassemia, even though the price is estimated to be $1.8 to $2.1 million per person treated, beti-cel does not exceed ICER's budget threshold of $734 million per year for a new treatment.

Recommendation: Advocates for better treatments for people with beta thalassemia – and their families – should consider making the following points in their written or oral comments:

- Even though ICER found that beti-cel produced very good improvements in ICER's costs-per-QALY gained, their use of QALYs as a fundamental basis for its cost effectiveness evaluation, continues to be problematic – particularly for people with chronic, serious health conditions or disabilities.

- Given what occurred in Europe, where government healthcare programs essentially prevented patient access to this curative treatment because of the high up-front costs, comments would be especially appropriate about the dramatic individual benefits, the overall cost-effectiveness (as demonstrated by ICER), and the small overall potential budget implications because of the very small number of people with transfusion-dependent beta thalassemia. Specific comments about ICER's potential budget impact analysis could also note that while ICER's formula is deeply flawed, its application in this case indicates beti-cel will not cause budget problems for the U.S. healthcare system.

- In the U.S., insurance companies are increasingly establishing very high co-payments or erecting other cost-based barriers – such as prior authorization or similar policies – that restrict access to new medicines. This is the U.S. equivalent of full denial of reimbursement that can occur in other countries that have a single or centralized healthcare financing structure. Advocates could raise concerns that even though beti-cel has been shown to provide significant clinical benefits and good economic "value," insurance companies could include difficult authorization processes designed to burden patients and their clinicians and prevent patients from obtaining this curative treatment.

Conclusions

- Summarize and restate your thoughts. Highlight the dramatic clinical benefits of beti-cel treatments and the great economic value beti-cel provides for patients and society by eliminating the need for frequent transfusions, “untethering” patients and their families from close clinical monitoring, and relieving the burden of receiving ongoing treatments.

- ICER will be developing a final report and having a public meeting. In your comments, consider asking ICER to strongly and clearly state its opposition to barriers erected by government regulators or payers that keep people with transfusion-dependent beta thalassemia from accessing beti-cel. Such treatment decisions should be made by the patient with their clinical team, and not based on whether a patient can access a needed treatment.