



Betibeglogene Autotemcel for Beta Thalassemia: Final Policy Recommendations

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Prepared for



Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the June 17, 2022 New England CEPAC public meeting on the use of betibeglogene autotemcel for the treatment of beta thalassemia. At the meeting, ICER presented the findings of its revised report on these treatments and the New England CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and one representative from a pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed [here](#), and a recording of the voting portion of the meeting can be accessed [here](#). More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found [here](#).

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility to facilitate meaningful patient access to curative therapies for beta thalassemia in ways that do not exacerbate disparities.

Stakeholder groups, including patients and clinicians, told us that optimum care is typically delivered in large academic medical centers or through Centers of Excellence. There are currently six programs in the US designated as Centers of Excellence in thalassemia care by the National Cooley's Anemia Foundation and only seven centers sponsored by the Centers for Disease Control and Prevention for the prevention of thalassemia complications. As such, it is probable that beti-cel will be accessible through specific facilities such as Centers of Excellence. Therefore, it is important that all stakeholders take steps to try to minimize the risk that access to beti-cel will only harden

the disparities (e.g., racial, geographic, health literacy) that characterize the United States (US) health care system.

Policy-makers and life science companies should consider that there are 300,000 people living with transfusion-dependent beta-thalassemia (TDT) worldwide, but only 1,000 of them reside in the US. Thus, the global burden of thalassemia lies predominantly outside of the US. Unfortunately, the current business model for innovation will not offer easy options for making expensive treatments accessible to the vast majority of patients living with TDT. Long-range policy efforts should be directed at addressing this important ethical problem.

To address these concerns:

Manufacturers should take the following actions:

- The manufacturer should work with existing Centers of Excellence and payers to ensure that people living with TDT who are eligible and interested in beti-cel have reasonable access to it, including considerations regarding non-English speaking patients, the need for travel, coverage for ancillary care, and out-of-pocket financial burden.
- If there are geographic regions poorly served by current Centers of Excellence, the manufacturer should work with clinical experts, patient advocacy groups, and others to expeditiously expand sites where beti-cel can be obtained.
- Engage with other life science companies and international policymakers to seek industry-wide actions to increase the availability of transformative therapies like beti-cel. Creative solutions should facilitate access to this therapy in lower income countries in a fashion that maintains incentives for innovation.

Payers should take the following actions:

- Consider the coverage for a service like beti-cel in a comprehensive fashion, including family need for travel, special needs of families who are not English speaking, ancillary care pre- and post-procedure, fertility preservation, and out-of-pocket financial burden. All elements must be addressed and aligned in order to reduce the risk that introduction of beti-cel will only worsen existing disparities in care for people with TDT.

Clinical specialty societies should take the following actions:

- Develop best practices around shared medical decision-making in order to facilitate meaningful patient access to a therapy that has a high likelihood of benefit, but still significant uncertainty around risks. Shared decision-making should also be done in such a way that it does not exacerbate disparities through attention to health literacy and incorporation of cultural competencies into provider trainings and patient-facing materials.

Payers

Recommendation 1

Should the announced price for beti-cel confirm assumptions that it will be priced in alignment with its likely benefits, 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.

Although beti-cel has strong evidence of substantial short-term net health benefit, given the existence of alternative first-line curative therapy (i.e., HSCT) and uncertainty around longer-term safety and durability, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria should be based on the FDA label, clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers and patients. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: <https://icer.org/wp-content/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage--September-28-2020.pdf>.

Drug-Specific Considerations

Payers should realize that patients will need treatment coverage that may only be accessible in specific medical centers and coverage policies should reflect that many patients and their families will need to travel significant distances to receive therapy. A patient's geographic area should not undermine the tenets of fair access to which all patients have a fundamental right.

Payers must consider coverage of fertility preservation in concert with coverage of beti-cel. Both patient representatives and clinical experts noted that future fertility is a key consideration in management. There are many complex issues regarding fertility (e.g., prepubescent patients, ongoing storage). Payers must be pro-active and transparent about what will be covered.

Coverage Criteria

- **Age:** Industry experts suggested that many payers will follow any labelled age restrictions for beti-cel. Trial participants were between the ages 4 – 35, but if the FDA label does not stipulate an age cutoff, clinical experts advised that younger patients might not have sufficient cells to donate, but this is a factor related to weight, not age. Clinical experts also advised that older patients were more likely to have other comorbidities, including iron overload, but that it would not be reasonable to identify a specific upper age limit. Under the assumption that beti-cel will be provided at a Center of Excellence, the general opinion across clinical experts and payer representatives was that payers should allow clinicians wide latitude to determine clinical eligibility. If age limits are recommended in the FDA label, however, payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients whom clinicians deem suitable candidates that are near the cutoff for the age necessary for coverage.
- **Clinical eligibility, transfusion dependence:** Consensus among policy round table clinical experts and criteria from clinical trials indicated that a threshold of eight transfusions or more per year is an acceptable definition of transfusion dependence.
- **Clinical eligibility, first-line HSCT unavailable:** In addition to age and evidence of transfusion dependence, payers are likely to require that patients do not have accessibility to a sibling-matched hematopoietic stem-cell transplantation (HSCT) as first-line therapy. Policy roundtable experts thought that attestation by a provider that a sibling-matched HSCT was not accessible would be sufficient and that it would be unreasonable to request proof of diagnostic tests from family members.
- **Exclusion criteria:** Clinical experts felt that patients with evidence of severe iron overload or serious medical comorbidities that would preclude eligibility for myeloablative chemotherapy should be excluded from eligibility. There is no recommended quantitative laboratory cutoff or imaging standard that defines a level of severe iron overload that would make a patient ineligible for beti-cel. As with other elements of eligibility, policy roundtable members felt that treating clinicians at a Center of Excellence should be allowed to evaluate iron overload among other factors in determining clinical eligibility.

Manufacturers

Recommendation 1

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.

The manufacturer of beti-cel deserves praise for the transparency with which it has discussed how it will value and price this treatment. Valuing new interventions in reasonable alignment with their added benefits for patients and families is a foundation for affordable access that retains the necessary incentives for meaningful innovation. However, with potentially transformative single-time therapies, traditional methods of cost-effectiveness analysis capture all the estimated lifelong downstream benefits of treatment, including not only health gains but the potential for reducing or eliminating massive costs of chronic treatment over many years. Thus, potential cures for expensive chronic conditions, such as beta-thalassemia and hemophilia, can be valued at extremely high one-time prices.

There is nothing wrong with acknowledging the substantial potential for cost offsets in the health system and beyond that may come with transformative therapy. However, assigning all that value in the pricing of treatments raises two fundamental questions. First, should the potential cure for an “expensive” condition be valued exponentially more than a potential cure for a condition that is less expensive, perhaps because it is rapidly fatal and does not accrue high costs over many years? And second, should the pricing of the therapy allocate to manufacturers “all” of the societal value at the incremental cost-effectiveness threshold, particularly when these kinds of treatments are far less likely to ever face generic competition that drives lower pricing?

We believe these two questions make it very reasonable for manufacturers, payers, and other policymakers to consider alternatives to full valuation of potential cures based on 100% of cost offsets being assigned to the price of the treatment. There is no normative policy regarding whether a 50%-50% sharing of cost offsets or some other level is most appropriate. Further policy development is needed in this area, but as single-time potentially curative treatments start to come to market, all stakeholders should be aware that different cost-effectiveness scenarios should be considered in arriving at judgments about the ultimate “fair” price for these therapies.

Recommendation 2

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.

Outcomes-based agreements are an important part of managing the uncertainty associated with [high-impact single or short-term therapies](#). In an outcomes-based contract, the manufacturer will return some payment to the payer based on clinical metrics of success or failure at one or more time points. Our policy roundtable discussion of the prospects for outcomes-based agreements for beti-cel emphasized the following points:

- The accepted measure of treatment success with beti-cel – freedom from transfusion – is notable for the relative ease of tracking through claims and other forms of medical record data, making beti-cel among the most promising treatments for an outcomes-based agreement.
- Nonetheless, many important definitions and other factors will need to be sorted out, including:
 - a) The definition of failure to achieve transfusion independence and of loss of transfusion independence. It would be appropriate to use the trial definition that transfusion independence is achieved if, within two years after administration of beti-cel, a patient needs no transfusions for 12 months. It also appears reasonable to consider that after this point, needing transfusions on either one or two occasions signals loss of transfusion independence.
 - b) How will large payments (e.g. 80% of \$2.1 M) be handled between the manufacturer and the payer, with all the complications of provider intermediaries?
 - c) How will payments be managed through the complexity of 340b payment structures?
 - d) How will clinical data integrity and data sharing between the payer and manufacturer be managed?
 - e) How will the payment agreement avoid triggering Medicaid Best Price regulations?

Recommendation 3

Given the complexity of outcomes-based agreements, and the large amount of money at stake in the case of beti-cel, payers and the manufacturer should consider creating or collaborating with some form of centralized process for defining clinical outcome measures to be used in these agreements in a way that would simplify the process without raising anti-trust concerns.

Clinicians and Clinical Societies

Recommendation 1

Update treatment guidelines for patients with TDT to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients, and payers.

At the time of introduction of beti-cel, clinical societies should rapidly update their practice guidelines for managing patients with TDT. Payers base their coverage decisions and integration of utilization tools to a great extent on clinical guidelines. The American Society of Hematology (ASH) has current guidelines for other hemoglobinopathies, but not beta thalassemia. However, ASH has endorsed guidelines on red blood cell specification for patients with hemoglobinopathies, including beta thalassemia, from the International Collaboration for Transfusion Medicine Guidelines.¹ Policy round table participants also highlighted that guidelines should be evidence-based and not consensus-based, and that formal algorithms would be helpful to inform medical decision-making.

Patient Organizations

Recommendation 1

Patient organizations have a vital role to play to promote objective descriptions of the risks and benefits of new therapies in order to support shared decision making for every patient. In addition, patient groups have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Advocacy and support groups helping people living with TDT should endeavor to educate patients about the potential risks and benefits of new therapies, particularly those with the potential for substantial harms, and work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. Patient groups for thalassemia, such as the Thalassaemia International Federation and the Cooley's Anemia Foundation, have developed educational materials for patients on current treatments. This should be expanded to provide additional guidance on gene therapy when it is made available as therapy. Patient groups might also design novel tools to help patients and providers engage in shared decision making, such as a compendium or video library of patient and caregiver experiences. Patient groups should also accept responsibility to publicly promote access and fair pricing of new therapies. For example, the Thalassaemia International Federation has made [public statements](#) on the cost and accessibility of gene therapy.

Researchers/Regulators

Recommendation 1

Data follow-up from cohort studies and real-world evidence are needed to further establish safety and long-term durability of beti-cel.

The small sample sizes of the current trials create uncertainty around serious, but rare harms such as mortality and myelodysplastic events. Additional data are needed to ascertain how beti-cel and its related conditioning regimen will perform over time and in the real world. Additionally, durability and the potential for life-time efficacy, can only be established with sufficiently long follow-up. To date, the earliest trial participants achieving transfusion independence are at about seven years of follow-up.

Recommendation 2

Additional clinical trials are needed to compare the safety and efficacy of beti-cel to current standard of care (hematopoietic stem cell therapy [HSCT]).

In the absence of clinical trial data, clinicians, patients, and medical decision-makers (e.g., parents or guardians), and payers are likely to continue to consider HSCT with a sibling-matched donor as the gold standard for eligible patients. However, there is reason to believe that beti-cel may be less risky than traditional HSCT given that it does not impose a risk of graft-versus-host disease or rejection. Despite these risks, advances in HSCT have lowered the risk of this procedure over time and evidence would likely be needed for gene therapy to supplant HSCT as standard of care.

References

1. Compernelle V, Chou ST, Tanael S, et al. Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline. *Transfusion*. 2018;58(6):1555-1566.

Appendix

Appendix tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the Friday, June 17, 2022 public meeting of the New England CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Francesca Beaudoin, MD, PhD, MS , Senior Medical Advisor, ICER	Maggie O’Grady , Program Manager, ICER
Jon Campbell, PhD, MS , Senior Vice President of Health Economics, ICER	Steven D. Pearson, MD, MSc , President, ICER
Noemi Fluetsch, MSc, MPH , Research Assistant, HEOR, ICER (Former)	Marina Richardson, MSc , Health Economist, ICER
Belen Herce-Hagiwara , Research Assistant, Evidence Synthesis, ICER	David Rind, MD, MSc , Chief Medical Officer, ICER
Victoria Lancaster, PharmD, MSc, MBA , HTA Fellow, ICER	Grace Sternklar, Program and Event Coordinator , ICER
Max Lee, PharmD , Pharmaceutical Intelligence Manager, ICER	Patty Synnott, MS, MALD , Project Director, Global Health Initiatives, Center for Evaluation of Value and Risk in Health

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member’s household) in any company with a product under study, including comparators, at the meeting in excess of \$10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC*	
Robert H. Aseltine, Jr., PhD Professor and Chair, Division of Behavioral Sciences and Community Health Director, Center for Population Health, UCONN Health	Aaron Mitchell, MD, MPH Assistant Attending, Memorial Sloan Kettering Cancer Center
Austin Frakt, PhD Director, Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System Professor, Boston University School of Public Health	E. Mylonakis, MD Chief of the Infectious Diseases Division and Dean’s Professor of Medicine, Warren Alpert Medical School of Brown University
Claudio Gualtieri, JD Undersecretary of Health and Human Services, Office of Policy and Management (OPM)	Brian P. O’Sullivan, MD Professor of Pediatrics, Geisel School of Medicine, Dartmouth College
Rebecca Kirch, JD Executive Vice President, Health Care Quality and Value for the National Patient Advocate Foundation (NPAF)	Jeanne Ryer, MSc, EdD Director, NH Citizens Health Initiative
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member’s household) in any company with a product under study, including comparators, at the meeting in excess of \$10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Monica Bhatia, MD , Associate Professor of Pediatrics and Director, Pediatric Stem Cell Transplant Program, Columbia University Medical Center	None.
Nathan Connell, MD, MPH , Associate Professor of Medicine, Harvard Medical School, Brigham and Women’s Hospital	Dr. Connell has received funding in excess of \$5,000 from Takeda Pharmaceuticals.
Leslie Fish, PharmD , Senior Vice President, IPD Analytics	Dr. Fish is a full-time employee of IPD Analytics.
Priyanka Kumar , Beta Thalassemia Patient and Advocate	None.
Clark Paramore, MSPH , Head of Value Demonstration, bluebird bio	Clark is a full-time employee of bluebird bio.
Erik Schindler, PharmD, BCPS , Director, Emerging Therapeutics and Outcomes-Based Contracting, UnitedHealthcare Pharmacy	Dr. Schindler is a full-time employee of UnitedHealthcare.
Eileen Scott , Patient Services Manager, Cooley’s Anemia Foundation	None.