Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value

Response to Public Comments on Draft Evidence Report

June 2, 2022

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Manufacturers		
bluebird bio		
1.	ICER should update its base-case value for beti-cel treatment success (i.e., TI: transfusion independence) to 90.2%, based on the latest available data and predictive modeling. Based on data recently presented at the Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR or "TANDEM Meetings" in April 2022, as of the August 2021 data cut, 38 patients treated with beti-cel in our Phase 3 studies are now TI evaluable (see definition below), 34 of whom have achieved TI. This success rate is 34/38 or 89.5%. All patients who have achieved TI have maintained their TI status (see Figure 1). In addition, internal analyses have shown that HbA^{T87Q} values were stable and durable by month 6, and predictive of achieving TI success for <u>ALL 34 patients</u> who have achieved TI status to date. For the remaining 3 non-evaluable patients who have not yet had sufficient follow-up time to be evaluable for the TI end point, the predictive probability of achieving TI for <u>ALL 3</u> (based on HbA^{T87Q} at month 6) is at least 99%, which would lead to a final phase 3 study TI <u>success rate of 37/41 or 90.2%.</u> ○ TI is defined as a weighted average Hb ≥9 g/dL without any pRBC transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion. ○ Please note as per the study statistical analysis plan, the pre-specified definition for TI-evaluable is defined as patients who have completed their parent study (i.e., 24 months of follow-up), or achieved TI, or will not achieve TI in their parent study. A patient is deemed 'will not reach TI in the parent study' if he/she is receiving chronic transfusions after 324 days of follow-up (<14 months of follow-up left in parent study), or if his/her Hb level never reached t0 (Hb ≥9 g/dL with no transfusions in the preceding 60 days) by 385 days of follow-up.	Thank you for sharing these updated data. The ICER Evidence Report has been updated to reflect the additional two patients who achieved transfusion independence between the posting of the Draft Evidence Report and the Evidence Report. The base-case input used in the economic model has been changed to 34/38 (89.5%). Our optimistic scenario analysis continues to use a TI success rate of 90.2% (37/41).
2.	The base-case value for beti-cel durability loss should be 0%, with a separate but scientifically plausible scenario considering potential, non-zero durability loss. This assumption is aligned with the known clinical evidence base and leading scientific	We had a number of discussions with experts about this and heard that it would be possible for patients to revert to TD if the population of infused stem cells that were not genetically modified became clonally dominant; it was felt

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	expertise, which should serve as the primary sources upon which to extrapolate the durability of beti-cel treatment effect. bluebird bio appreciates that for the Draft Report ICER lowered the "loss of beti-cel durability" assumption included in its Modeling Analysis Plan to a value of 0.271% starting at Year 7. However, the known evidence base to date (up to ~ Year 7) has indicated no loss of durability or expectation of loss of durability by investigators; and leading scientific experts (who have separately submitted their responses to ICER) expect lifetime durability. We strongly encourage ICER to use a base-case value that reflects both the available evidence and leading scientific expertise rather than a more theoretical assumption. We recognize that scenarios on lapse of durability will be evaluated by ICER but believe such scenarios should be secondary to the base-case. *Additional points* Independent experts agree that following successful engraftment and achievement of TI, the effects of beti-cel are expected to be life-long. • See the European Medicines Agency (EMA) summary of product characteristics for beti-cel (referred to as Zynteglo) • Tucci et al. (2021) indicate that the lentiviral vector integrates into hematopoietic stem cell genome and provides long-lasting functional copy of the defective gene	that over a lifetime post-treatment, an estimate of 10% reversion was fair. An estimate of no reversion was explored in an optimistic scenario.
3.	The currently available evidence on the durability of beti-cel are more robust than evidence from prior ICER reviews of gene therapies, which assumed lifetime benefit. For example, in one of the gene therapy reviews, ICER's base-case scenario allowed for lifetime durability of the gene therapy when: • the longest follow-up was just 2 years (versus up to 7 years for beti-cel as of August 2021 data cut) • sample size was notably smaller (n=12 in one of the gene therapy trials which was basis for ICER base-case) than that of the current beti-cel data package (discussed above) • ICER relied upon that gene therapy's primary efficacy measure for its durability assumption, and it was considered a surrogate endpoint for future developmental milestones. In contrast, beti-cel's primary efficacy measure of TI is considered a direct clinical endpoint.	ICER assessment teams consider the disease context, the evidence, the mechanism of action, and many other factors such as expert opinion when forming the economic model assumptions around the lifetime durability of treatment. We note that within the ICER assessments for hemophilia and retinal disease, we did not assume long-term durability. Long-term durability decisions are made on a case-by-case basis after careful consideration.

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4.	ICER's model incorrectly assumes a correlation between patient non-adherence and chelation costs, in the absence of data to support this assumption. TDT patient representatives have clarified that patients will continue to maintain their normal prescription refill patterns for chelators despite episodes of nonadherence. This aspect of the model should be removed. bluebird bio recognizes that the current standard of care for individuals with TDT includes multiple iron chelation therapy options, each with their own advantages and disadvantages. We also recognize there is a known problem with individuals with TDT being able to maintain good adherence with their iron chelation therapy. However, we are not aware of any published evidence that indicates a direct correlation between poor adherence with iron chelators and prescription refill patterns for those iron chelation therapies. In our discussions with individuals who live with TDT, iron chelation therapy has been a long-standing chronic routine, and prescription refills are automatic and ongoing. In addition, a recently published cost of care study for β-thalassemia found iron chelation therapies were a major cost driver, and the annual total average costs for chelation therapy were indicative of ongoing refills for TDT patients.	It is likely not 100% of patients will be on an automatic refill for their chelation prescriptions for their lifetime. Patients likely go through many insurance changes and also likely go through many chelation medication changes over their lives. 80% adherence is considered high for many chronic therapies. We suggest that 95% adherence, if anything, is likely optimistic and may result in simulating increased cost offsets for interventions that obviate chelation therapy compared to real practice.
5.	bluebird bio would like to clarify that any potential outcomes-based payment plan for beti-cel that is modeled by ICER should include a payback option of up to 80% if treatment with beti-cel is unsuccessful. In its Scenario Analysis 4 in the Draft Report, ICER found that the incremental-cost effectiveness ratio would increase to $133,900 with a scenario where the full cost of beti-cel was paid at time of transplant (i.e., Year 1 in model). However, ICER does not include the modeled outcomes agreement (i.e., payback up to 80% if treatment fails) in this scenario. bluebird bio plans to offer an outcomes agreement for beti-cel treatment failure that is separate and distinct from the specific payment plan (e.g., pay all upfront vs. pay over time) that may be contracted with health insurers. We want to clarify that any model scenarios run by ICER should include an assumption that bluebird bio will pay back up to 80% if a patient treated with beti-cel does not achieve TI.	In the revised report, the base case assumes a full upfront payment of $2.1M with bluebird bio's suggested outcomes-based agreement. We continue to include a scenario without an outcomes-based agreement as some consumers of our work may find this analysis helpful for policy making (e.g., in cases where outcomes-based agreements are not feasible).
6.	In addition, we have provided suggestions/corrections for wording changes, citations and clinical data (as part of the Appendix) in the clinical section of the Draft Report. To summarize:	We have updated the text and references.

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	• Patients with beta-thalassemia receive transfusions and iron chelation as a part of standard of care; Phlebotomy refers to withdrawal of blood. We suggest you change 'phlebotomy' to 'iron chelation' on Executive Summary page ES1 and Patient and Caregiver perspectives page 3. • We have added several reference-related comments, so the statements are cited to appropriate references. • Please note, study HGB-212 study enrolled b0/b0 and non-b0/b0 pts. Non-b0/b0 pts (included IVS-I-110 homozygous and IVS-I-110/b0 genotypes) enrolled had severe genotypes similar to b0/b0 pts. • We have added comments to edit data included in Table 3.1, 3.2, D6 & D7.	
Vertex Pharmaceuticals		
1.	We appreciate the recognition of the profound impact that transfusion-dependent beta-thalassemia (TDT), the most severe form of the disease, has on patients and their caregivers, encompassing both physical and psychosocial aspects of life. As acknowledged in the draft evidence report based on patient input, the existing standard of care, largely composed of lifelong blood transfusions and iron chelation therapy, is insufficient and burdensome; and the unmet medical need for a transformative therapy of this debilitating disease is paramount. We are encouraged to see ICER's recognition of the clinical value of one-time potentially curative gene therapies for TDT that are likely to transform the treatment paradigm for these patients and society at large. In the economic evaluation, it is evident that these types of therapies have the ability to improve quality and length of life and reduce the substantial costs associated with current standard of care for this debilitating disease. Considering the significant total healthcare cost of TDT is currently estimated at $5.4 million over a patient's lifetime, gene therapies with the potential to cure can not only improve patient outcomes, but also help alleviate the overall economic burden to the healthcare system by averting the costs associated with the lifelong management of the disease.	We agree that gene therapies can offer substantial benefits to patients and health systems. We encourage manufacturers to consider gene therapy prices that can help alleviate the overall economic burden to health care systems while improving health.
2.	The clinical value of a therapy is independent of any particular payment model; we believe that a variety of coverage solutions may be valuable in supporting patient access to innovative therapies.	We agree that clinical value is independent of payment models. We gave beti-cel an evidence grade of B+. ICER believes in a grand bargain where we can achieve fair pricing, fair access, and future innovation. We agree that

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		a variety of coverage solutions can support this grand bargain.
Patients/Patient Groups		
Cooley's Anemia Foundation		
1.	Thank you for the thorough and detailed draft report. The Foundation is pleased that the report emphasizes the potential lifetime benefit of the procedure under discussion, as well as acknowledges more intangible variables of importance (such as social impact, etc.)	Thank you.
2.	The Foundation wishes to re-emphasize that, while individuals with thalassemia are living much longer lives if they are able to receive optimal treatment, life expectancy still continues to lag behind the average. Over the 10-year period 2011-2021, of patients included in the Cooley's Anemia Foundation patient database, for those patients who passed away for which age was known, the average age of death was 40.12 years; for those who were classified as transfusion-dependent-thalassemia, the average age was 33.99 years (median age of 37 years). An effective and safe curative approach is an option which would be of great interest to many members of the thalassemia community. Thank you for your interest in this area.	Thank you for this comment, we have added text to reflect this information.
Thalassaemia International Federation		
1.	A most comprehensive, well-designed, and expressed document, the Draft Evidence Report developed by ICER constitutes a state-of-art objective representation of evidence, considerations and assumptions concerning betibeglogene autotemcel for beta thalassemia. It is indeed commendable that the inclusion of the patient perspective has been pursued every step of the way and that the independent panel of experts has focused on the clinical value of gene therapy for thalassemia in its own merit, and not, as others have done previously, in comparison to the standard clinical management provided to patients. The effort made to provide clarity, openness and in ambiguity through the review of evidence as well as taking into consideration the societal and personal burden of disease finds us in agreement, and we applaud the report conclusion outlining that despite the uncertainties (as explained in depth within the document), betibeglogene autotemcel for beta thalassemia should be at least provided as a choice to patients.	Thank you for this comment. While our report is focused on beti-cel within the US health system, we strongly hope that global manufacturers and payers can come to agreements that increase access to this therapy for the large proportion of patients with thalassemia who do not reside in the US.

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	The safety and efficacy of betibeglogene autotemcel for beta thalassemia has been demonstrated by the approval of the European Medicines Agency (EMA) in 2019 and we are confident will be recognized by the Federal Drug Administration (FDA) in due course. Facilitating the accessibility and availability of betibeglogene autotemcel for beta thalassaemia following regulatory approval will enable the collection of real world evidence, which will further corroborate this report conclusion and if required its adjustment. The Thalassaemia International Federation – an organization representing the voice of thalassemia patients in over 68 countries, including the USA, for more than 30 years, supports the right of each and every patient to be provided the opportunity to choose to undergo (or not) betibeglogene autotemcel. We hope that this decision-making process, will encourage other countries will proceed with their own assessment of betibeglogene autotemcel for beta thalassemia, realizing its ultimate value for the patients and thus making it available and accessible to their own populations. Hence, TIF remains fully committed to continuing its efforts to enable the accessibility of gene therapy for thalassemia patients as a choice and therefore supports ICER's efforts for providing a complete report on the value of betibeglogene autotemcel as compared to standard of care services for beta thalassemia, realizing its ultimate value first and above all for the patients.	
Other		
PIPC		
1.	ICER continues to use the discriminatory Quality-Adjusted Life Year (QALY). As PIPC has commented previously, the use of discriminatory metrics, including the QALY, is inappropriate and too often results in a discriminatory impact. It is acknowledged that QALYs discriminate by design against people with disabilities and chronic illnesses. There should be no room for discrimination in health care decision making, and we urge ICER to cease use of discriminatory metrics.	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues you raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.
2.	ICER's model takes a narrow perspective. The narrow perspective of ICER's model ignores the wider benefit of reduced demand on scarce health care resources, which	Thank you for calling our attention to the potential opportunity costs of blood transfusions used for

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	overlooks a valuable facet of successful treatment of transfusion dependent beta thalassemia (TDBT). TDBT patients account for a larger percentage of blood transfusions around the world. TDBT patients make up almost 18% of all blood transfusions in Greece, and almost 10% in Hong Kong. This is expected to rise to 30% by 2024. In the United Kingdom it is expected that the demand for blood products for TDBT patients is likely to rise by 20% in the next five years. The European Committee on Blood Transfusion reported that most of the 45 countries evaluated had a nationally coordinated blood program (85%), but 25% of countries, including many countries with a high prevalence of hemoglobinopathies such as BT could not meet their national need for blood supplies. The red blood cells required for blood transfusions are a finite resource. Given this reality, the successful treatment of people living with TDBT would lead to benefit for patients with other blood disorders, as it would be less likely they would face shortages of necessary red blood cells. This system wide value gain is not incorporated into standard cost-effectiveness modeling, and this narrow perspective ignores the effects of redistribution of scarce natural resources. It is not unprecedented to construct a model that captures a treatment's broader impact on the health care system. There have been studies evaluating the wider public health value of successful treatment of hepatitis C and the resulting impact on the freeing up of essential organs for transplant and the resulting health gain to patients with conditions other than hepatitis C in the healthcare system. To fully capture the societal value of gene therapy in TDBT, economic models should also capture the value of reduced supply-demand shortfall for blood products in the healthcare system and the lives saved as a result.	transfusion dependent beta thalassemia. We have added this concept to our potential other benefits section (Section 5) in our revised report.
3.	ICER uses a Decision-Tree Markov Model to estimate cost-effectiveness, whereas a Time-To-Event Methodology would be a more appropriate mechanism. ICER's model is centered on transfusion dependence: how often transfusions were required and how long a patient went without needing a transfusion. Given this desired outcome, the most effective model for comparing two scenarios (with and without gene therapy in this example) would be a time-to-event methodology such as a discrete event simulation model (DES) or a discretely integrated condition event (DICE) model.	We expect that an alternative but appropriate model structure would result in similar findings to those presented in the evidence report. This is based on a model replication exercise that we conducted in comparison to the findings published using the DICE methodology approach. Our replication findings are presented in the evidence report supplement. This replication exercise gave us confidence that a Markov

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	The one published economic evaluation of gene therapy treatment in beta thalassemia used a DICE methodology and uses largely the same sets of inputs as the ICER model but its conclusion was that beti-cel was much more cost-effective than that estimated by the ICER model. These methods also allow for the integration of a wider set out of outcomes of interest throughout the course of the disease and the lifetime of the patient being simulated, which would help alleviate the problem with the ICER model's overly limited concentration on one aspect of the patient journey, transfusion dependence.	model structure would yield comparable results to the published DICE model, given the same set of model inputs used. We are surprised that PIPC seems to endorse the published economic evaluation of gene therapy treatment in beta thalassemia that used the DICE method. We note that this DICE-based model also relied on the "discriminatory QALY." Finally, ICER shared a draft model with the manufacturer during the public comment period and welcomed feedback that would improve the model.
4.	The mortality ratio for transfusion dependent beta thalassemia used in the model is at the low end of recent estimates. The model developed uses 3.5 as an estimate of the standardized mortality ratio (SMR) for transfusion dependent patients – or patients in periods of transfusion dependence. Other estimates of the SMR in the literature range from 6.2 to 13.5. This likely means that the value of reducing need for transfusions and the reduction of patients in the transfusion-dependent states would have a much higher mortality impact than is currently reported in the draft ICER report.	Other health technology assessment models and the model that beti-cel's manufacturer sponsored all used SMR findings around 3.5. We added text to recognize that mortality estimates lag improvements in treatment (e.g., improvements in chelation therapy).
5.	The number of transfusions used in the model is likely low. ICER's model assumes that patients under 18 years of age have an average of 14.95 transfusions per year, and patients 18 years of age or older have an average of 16.1 transfusions per year, which is based on MarketScan data reported in Kansal 2021. Other studies suggest this might be an underestimate of the burden of TDBT. Recent studies suggest 17-41 transfusions per year. It is essential that ICER's model accurately reflect the patient experience, so we would encourage ICER to revisit these inputs to assure it is captured correctly.	We used estimates consistent with the model that beti-cel's manufacturer sponsored. Without citations, we cannot critically assess differences across transfusion estimates.