December 16, 2021

betibeglogene autotemcel Review Team
Institute for Clinical and Economic Review (ICER)
14 Beacon St, 8th Floor
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RE: bluebird bio's response to the proposed scope for ICER's value assessment of betibeglogene autotemcel (beti-cel) for transfusion-dependent beta thalassemia (TDT)

Dear ICER Review Team:

bluebird bio appreciates the opportunity to participate in ICER's evaluation of beti-cel for the treatment of TDT. We are pleased to submit feedback on this review's draft background and scope published on November 24, 2021. ICER's description of the severity of TDT, and its associated complications, impact on quality of life, and burden of being tethered to the healthcare system was well characterized. bluebird bio offers recommendations on the draft scope with the belief that our input will enhance the accuracy of this review and meaning to its intended audience and all involved stakeholders.

Below are key recommendations, along with associated rationale for each, for ICER to consider when finalizing the scope for this review.

1. beti-cel is in development for TDT only; ICER's ultra-rare framework should also apply for this review
2. Use a life-time horizon for all scenarios; avoid scenario analyses that inappropriately truncate the time-horizons when evaluating the cost-effectiveness of beti-cel
3. Avoid sub-group analyses based on genotype, as TDT treatment and associated outcomes are not expected to vary by genotype.
4. A microsimulation modeling approach should be undertaken for this economic evaluation
5. Additional point of clarification regarding disease and treatment background

1. beti-cel is in development for TDT only; ICER's ultra-rare framework should also apply for this review

beti-cel (previously known as LentiGlobin™ for TDT) is a gene-addition therapy being investigated for the treatment of TDT and is a separate gene therapy product than lovotibeglogene autotemcel ('lovo-cel'), which is being developed by bluebird for sickle cell disease (SCD). It is not possible to use beti-cel to treat a patient with SCD, or to use lovo-cel to treat a patient with TDT. It would be neither safe nor effective.

The 2 gene therapy products are manufactured using distinct starting material. While both are manufactured using patient HSPC (hematopoietic stem and progenitor cells) and the same lentiviral vector component (BB305 LVV), the HSPC apheresis starting material collected from patients with SCD and mobilized using plerixafor alone, have different attributes than the HSPC apheresis starting material obtained from patients with TDT that are mobilized using GCSF (granulocyte colony-stimulating factor) and plerixafor. Because of these differences, the manufacturing process and associate parameter ranges are different for the 2 substances. Both the

United States Adopted Names (USAN) Council of the AMA and the WHO have assigned separate nonproprietary names for beti-cel and lovo-cel[1,2].

The FDA guidance 'Interpreting the Sameness of Gene Therapy Under the Orphan Drug Regulations' acknowledges there are various features that can contribute to the therapeutic effect of a gene therapy product. These additional features may include the cell type that is transduced. The FDA intends to determine whether 2 gene therapy products are different drugs on a case-by-case basis[3]. Accordingly, the FDA has acknowledged lovo-cel as a unique gene therapy product; in April 2020 the FDA accepted the future planned BLA submission of lovo-cel for SCD as a separate BLA (versus a supplemental BLA to beti-cel).

It is estimated that approximately 1,400 people in the US have TDT[4,5]. Therefore, all elements of the ICER Value Frameworks for *both* high impact single and short-term therapies (SSTs) and for ultra-rare disease should apply for ICER's review of beti-cel.

2. Use a life-time horizon for all scenarios; avoid scenario analyses that inappropriately truncate the time-horizons when evaluating the cost-effectiveness of beti-cel

We appreciate that ICER recognizes the base-case for a comparative value analysis should incorporate a lifetime time horizon, as it is expected that the clinical and economic benefits of beti-cel will be realized in the long-term through the avoidance and/or significant reduction of systemic complications of transfusion-induced iron overload[6].

As of August 18, 2021, approximately one-third of patients treated with beti-cel in clinical studies have at least 5 years of follow-up. All patients who achieved transfusion independence (TI) have maintained TI as of last follow-up[7].

The effects of beti-cel are expected to be life-long, a notion accepted by regulatory agencies[8]. Treatment results in the establishment of a population of undifferentiated stem cells in the bone marrow that serve as a long-term reservoir for red blood cells (RBCs) that have the functional β-globin protein and possess the capacity for long-term self-renewal.[9,10,11,12]

We strongly believe a lifetime time horizon should be used in all scenarios. If ICER does pursue scenarios evaluating durability of effect of beti-cel, we recommend utilizing a decay curve over time (i.e. a proportion of patients do not maintain response with proportion increasing over time) as this is more consistent with scientific understanding of HSCs. This approach was acknowledged as appropriate by experts in health economic modeling and β-thalassemia[13]. This approach is also consistent with available data from the clinical trials, beti-cel's mechanism of action, and the proposed long-term value of beti-cel to the health system.

3. Avoid sub-group analyses based on genotype, as TDT treatment and associated outcomes are not expected to vary by genotype.

As correctly noted by ICER, β-thalassemia is 'categorized into 2 main groups based on clinical severity and transfusion requirement regardless of genotype: TDT and non-TDT (NTDT)'[14].

Clinical management is determined by disease severity, hemoglobin levels, and transfusion burden, and is not based on genotype[15]. Mirroring this, beti-cel is intended to treat TDT irrespective of genotype. Moreover, the primary beti-cel outcome of TI is not expected to vary by genotype[16]. Given genotype is unlikely to be an important consideration for clinical

management and treatment outcomes, we do not recommend performing sub-group analyses by genotype.

4. A microsimulation modeling approach should be undertaken for this economic evaluation

As described in bluebird's comments to ICER's draft scope of its review of TDT in 2019, there is wide variability in risk of morbidity over time due to levels of iron overload in different tissues such as liver and heart and associated mortality outcomes based on many patient and treatment characteristics. This variability makes it very challenging to develop a cost-effectiveness model utilizing a Markov cohort approach[17]. Therefore, we recommend microsimulation modeling for the economic evaluation of beti-cel. This modeling approach for TDT was developed in consultation with experts in both β-thalassemia and health economic modeling and has been accepted for publication in a peer-reviewed journal[13].

5. Additional points of clarification regarding disease and treatment background

ICER appropriately characterized the background, current treatment paradigms, and burden of TDT in the draft scope. However, bluebird has a point of clarification regarding genotype versus disease classification that should be corrected in the final scope.

Patients with completely absent β-globin are considered to have a β0/β0 genotype, and usually have the most severe form of disease given their inability to produce any endogenous hemoglobin[18]. However, genotype classification is not synonymous with the *historical* phenotypic terminology of the sub-types 'β-thalassemia major' & 'β-thalassemia intermedia' (i.e. β+ subtypes can also be considered thal major, they are not just thal intermedia). The most appropriate and up-to-date classifications are TDT and Non-TDT (NTDT) which are genotype agnostic[14].

Kind regards,

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b colorful, b cooperative, b yourself

References:

1. Ama Finder, https://searchusan.amaassn.org/finder/usan/search/lovotibeglogene%20autotemcel/relevant/1/
2. International Nonproprietary Names for Pharmaceutical Substances (INN). World Health Organisation (WHO) Drug Information. 2021; 35, 2. Accessed at: https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl125.pdf?sfvrsn=af269747_5&download=true
3. Interpreting sameness of gene therapy products under orphandrug regulations. Guidance for Industry. Food and Drug Administration. September 2021. Accessed at: https://www.fda.gov/media/134731/download. Page 5 and 6 state: "*In instances where "2 gene therapy products express the same transgene and/or use the same vector, determining whether the gene therapy products are the same drug for purposes of 21 CFR 316.3(b)(14)(ii) may also depend on additional features of the final product that can contribute to the therapeutic effect. These additional features .....may include the cell type that is transduced. .....In these cases, FDA generally intends to determine whether the two gene therapy products are different drugs for purposes of 21 CFR 316.3(b)(14)(ii) on a case-by-case basis.*"
4. Hulihan et al. State-based surveillance for selected hemoglobinopathies. Genet Med 2015;17(2):125-130. doi: 10.1038/gim.2014.81
5. Vichinksy et al. Transfusion Complications in Thalassemia Patients: A Report from the Centers for Disease Control and Prevention (CDC). Transfusion 2014;54(4):972. doi: 10.1111/trf.12348
6. Public comments to proposed scope for ICER's value assessment of transfusion dependent β-thalassemia therapies. January 27, 2020. bluebird bio, Comment 4 stated: "*Patients with TDT require life-long blood transfusions as well as accompanying iron chelation therapy to address iron overload. The comorbidities and mortality resulting from anemia and transfusion-induced iron overload are evident in the short-term, but more so in the long-term trajectory of TDT. TDT has been shown to adversely impact survival and health-related quality of life and has contributed to significant economic burden to the health system. We expect that the clinical and economic benefits of LentiGlobin will be realized in the long-term through the avoidance and/or significant reduction of systemic complications of transfusion induced iron overload. Thus, estimating its cost-effectiveness using shorter time horizons such as five years, or even ten years, fails to convey its long-term benefits and overall value to the TDT patient community and the health system*."
7. Thompson A.A. et al. Restoring Iron Homeostasis in Patients Who Achieved Transfusion Independence After Treatment with Betibeglogene Autotemcel Gene Therapy: Results from Up to 7 Years of Follow-up [Conference presentation]. American Society of Hematology, Atlanta Georgia, 2021. Presentation # 573. Abstract available at: https://ash.confex.com/ash/2021/webprogram/Paper148177.html
8. Zynteglo (autologous CD34+ cells encoding βA-T87Q-globin gene). An overview of Zynteglo and why it is authorised in the EU. European Medicines Agency. May 2019. Accessed at: https://www.ema.europa.eu/en/documents/overview/zynteglo-epar-medicine-overview_en.pdf. Page 2 states: "*The effects of Zynteglo are expected to last for the patient's lifetime*."

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10. Mansilla-Soto J. et al. Cell and gene therapy for beta-thalassemias: advances and prospects. Human Gene Therapy. 2016 Apr;27(4):295-304. doi: 10.1089/hum.2016.037
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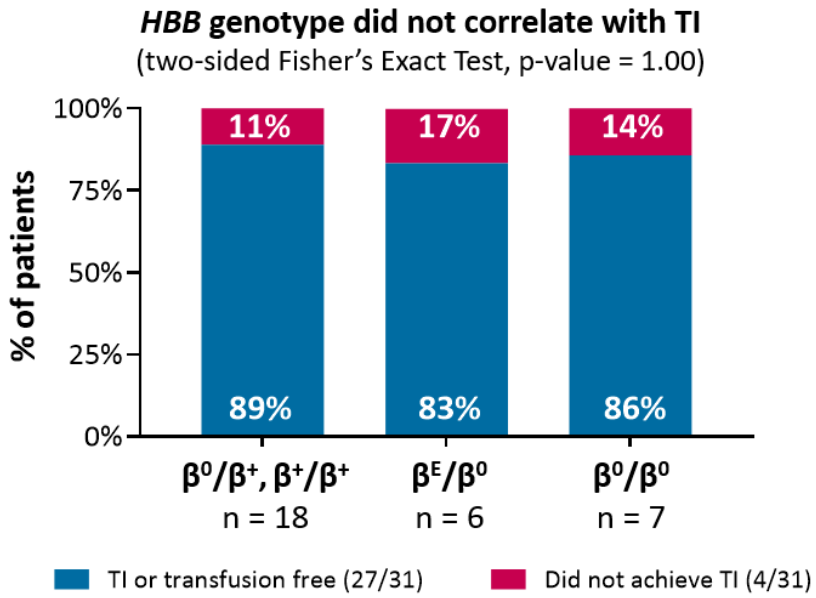
12. Dong AC & Rivella S. Gene addition strategies for B-thalassemia and sickle cell disease. Advances in Experimental Medicine and Biology. 2017; 1013:155-176. doi:10.1007/978-1-4939-7299-9_6
13. Kansal AR, Reifsnider OS, Brand SB, Hawkins N, Coughlan A, Li S, Cragin L, Paramore C, Dietz AC, Caro J. Economic evaluation of betibeglogene autotemcel (Beti-cel) gene addition therapy in transfusion-dependent β-thalassemia. Journal of Market Access & Health Policy. 2021. doi: 10.1080/20016689.2021.1922028
14. Cappellini MD, Farmakis D, Porter J, Taher A. Guidelines for the Management of Transfusion dependent Thalassaemia [TDT], 4th ed. Thalassaemia International Federation; 2021.
15. Chonat S and Quinn CT. Current standards of care and long term outcomes for thalassemia and sickle cell disease. *Advances in Experimental Medicine and Biology*. 2017; 1013: 59-87. Page 5 States: "The decision to begin chronic transfusion therapy is often based on clinical characteristics due to complex and incompletely understood genotype-phenotypes correlations in thalassemia [22]. Chronic transfusion is considered in thalassemia patients when the hemoglobin concentration is consistently below 6–7 g/dL, the anemia is symptomatic, quality of life is poor, growth and development is faltering, or there is troublesome extramedullary hematopoiesis. Early initiation of transfusions may also minimize the risk of alloimmunization [20, 23]."
16. Walters et al. Response of patients with transfusion-dependent β-thalassemia (TDT) to betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy based on HBB genotype and disease genetic modifiers. [Conference presentation]. American Society of Hematology Virtual Meeting 2020. Poster #1699. See Appendix, Figure 1 for details on TI by genotype
17. Public comments to proposed scope for ICER's value assessment of transfusion dependent β-thalassemia therapies. January 27, 2020. bluebird bio, Comment 3 stated: "*Iron overload and associated complications account for most of the morbidity and mortality in TDT. Iron levels are predictors of future outcomes, specifically cardiac, hepatic and endocrine morbidity and mortality. These morbidity and mortality outcomes can vary significantly based on age, gender, and treatment characteristics, namely transfusion history and requirement. Modeling such outcomes based on different ranges of iron overload that are dependent on individual patient and treatment characteristics would require a substantial number of health states if employing a Markov modeling approach and would render such a model highly complex. Conversely, simplifying the model with a limited number of health states will underestimate the magnitude of health and economic burden associated with transfusion and iron overload. Using a microsimulation modeling approach can address the complexities associated with modeling the nuances of events and timing of events associated with iron overload in TDT and appropriately evaluate cost-effectiveness of interventions assessed. We therefore*

recommend ICER consider employing a microsimulation modeling approach for this review."

18. Cao A, & Galanello R. Beta-thalassemia. Genet Med. 2010;12(2):61-76. doi: 10.1097/GIM.0b013e3181cd68ed

Appendix

Figure 1. HBB Genotype does not correlate with TI



Walters et al. ASH 2020 Virtual Meeting Poster #1699. Data as of 3 Mar 2020

Comments on Draft Background and Scope

From Craig Butler, Cooley's Anemia Foundation:

1. On page 1, when discussing populations most affected by beta thalassemia, you may want to add "South Asia," depending upon how you are defining "Middle East" and "Southeast Asia." This addition would make it clear that countries with significant beta thalassemia populations such as India, Pakistan and Sri Lanka are included.

2. As currently written, the beginning of the document does not adequately represent the range of complications typically associated with TDT. In addition to the already-mentioned pulmonary hypertension, liver dysfunction, cardiac manifestations), patients often contend with low bone mass, diabetes, growth and development problems, fertility and pregnancy issues, hypothyroidism, and risk of transfusion-related infections and reactions. Much of this is included later in the list of Outcomes, but it may help to include this in the background section as well.

3. Under the Applicable Framework Adaptations, I find the first section confusing. You state that you do NOT plan to assess beti-cel under the serious, ultra-rare conditions because it does not meet the criteria of having clinical trials in a patient population greater than 10,000, but then state that it IS being studied in sickle cell, with 100,000 patients – which IS indeed greater than 10,000. I may be misunderstanding this, or it may be that it is not phrased clearly.

4. Under Scope of Comparative Value Analyses, you state:

> The primary population for the economic assessment will be consistent with beti-cel trial populations (patients with TDT who are eligible for HSCT but do not have access to a matched donor).

This document does not go into detail defining HSCT eligibility, but I raise the question of the degree to which HSCT eligibility is consistent with patient eligibility for beti-cel treatment.

5. Under Potential Other Benefits and Contextual Considerations, I just wish to emphasize the importance of the potential benefits as listed in the second table. Although advances in care have enabled patients to make great strides in terms of career, family life, etc., most patients are still hampered to some degree by their thalassemia. For example, choice of college is impacted by availability of a nearby facility that can provide adequate treatment; the same applies to choice of job opportunities. Choice of a major and a subsequent career path may also be impacted by the presence of thalassemia, as individuals may perceive that their treatment needs or possible physical limitations related to their health may preclude some options.

Because of the extreme cost associated with thalassemia care management, patients and caregivers are also careful to choose employment which provides healthcare plans that will adequately cover their treatments. (This also means that patients and caregivers may continue to be employed in an employment situation which is not necessarily to their liking because of the availability of appropriate healthcare coverage.) Caregivers of pediatric patients, as well as adult patients themselves, must also seek employment situations that enable them to be absent from their workplace for regular transfusion visits; this often results in employment that is not their

first choice and in many instances in absenting themselves from the workforce. The need for regular transfusion appointments also impacts patients and caregivers financially in terms of costs associated with transportation and parking, arranging childcare for other children in the family, etc.

In addition, families that include one child with thalassemia and another or others who do not have thalassemia often encounter challenges when siblings feel to some degree left out or ignored because of all the time and attention required for the child with thalassemia. There may also be emotional challenges related to a child's feelings about the welfare of a sibling with a chronic disorder like thalassemia.

6. Under Identification of Low Value Services, you have already mentioned blood transfusions and I assume would also include a decrease in and ultimately hopeful elimination of iron chelation therapies. Other areas to consider might include:

- a decrease in frequency of monitoring of overall care;
- decrease in frequency of regular testing (such as serum ferritins);
- elimination of luspatercept for patients currently prescribed this therapy;
- once chelation therapy is eliminated, cessation of tests required in use of specific chelators (monitoring kidney function, hepatic function, neutrophil count, etc.);
- possible reduction in frequency of or possible elimination of MRI measurements of liver and cardiac iron;
- possible reduction in frequency of or possible elimination of DEXA scans and other tests related to low bone mass;
- increased availability of red blood cell units for other individuals needing blood;
- savings of time/labor from blood banks especially in terms of time spent searching for appropriate units (as many thalassemia patients have developed antibodies that make blood matching challenging);
- potential reduction in frequency of consultations with hospital social workers (assuming eventual reduction/elimination of transfusions and chelation results in fewer obstacles requiring aid of social worker);
- decrease in time spent by nurses and social workers on matters related to insurance coverage denials of treatments essential for thalassemia management (which in many individual cases can be very time consuming).

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13 December 2021

TO WHOM IT MAY CONCERN

Subject: Comments of the Thalassaemia International Federation (TIF) on the Draft Scoping Document concerning betibeglogene autotemcel for beta thalassaemia

Dear Sirs,

The Thalassaemia International Federation (TIF) takes the opportunity of this communication to provide its feedback, as representatives of the thalassaemia patient community, regarding the Draft Scoping Document dated 24 November 2021 developed by the Institute for Clinical and Economic Review (ICER) for betibeglogene autotemcel for beta thalassaemia.

A curative approach via gene therapy has been the enduring dream for more than three decades now by the thalassaemia patient community. Now that such an opportunity is within reach as a result of scientific advancements, but which may not be made accessible mainly due to economic reasons, without the patients' perspective being taken into account is truly unfathomable. Therefore, we would like to thank ICER for the opportunity to bring this aspect of the patient perspective to forefront.

At this point allow us to briefly introduce our Federation: The Thalassaemia International Federation (TIF) is a patient-orientated non-profit, non-governmental umbrella federation, established in 1986 with Headquarters in Nicosia, Cyprus. Our mission is to promote access to optimal quality care for all patients with thalassaemia worldwide. To-date membership boasts 240 members from 68 countries across the globe.

TIF works in official relations with the World Health Organisation (WHO) since 1996, enjoys active consultative status with the United Nations Economic and Social Council (ECOSOC) since 2017, is an official partner in the field of Health for the European Commission since 2018 and a member of the Committee of International NGOs of the Council of Europe since 2019.

Most remarkably, TIF has been awarded, in the context of the 68th World Health Assembly in May 2015, the *'Dr Lee Jong-wook Memorial Prize'* for the Federation's outstanding contribution to public health.

More information about the Federation is available at www.thalassaemia.org.cy

Among our founding members is the US-based Cooley's Anemia Foundation, that remains an active full member of our Federation and whose representatives have served on TIF's Board of Directors for more than 30 years. Together with the Cooley's Anemia Foundation we work to improve the quality of life and health outcomes of the approximately 1,379 people living with thalassaemia syndromes in the USA.

We note that TIF maintains a global epidemiological database of thalassaemia syndromes at its HQ that includes both prevalence and incidence rates per country, based on published scientific data but also on the reports/information received during our field work in more than 72 countries. The estimated number of patients in the USA, we believe is an underestimation considering the absence of a unified national registry and the global population movements especially from South East Asia to the West coast areas. The results of this work have been published in the Global Thalassaemia Review 2021.

Patient Perspective on Gene Therapy – TIF's findings:

The patient acceptability and expectations of gene therapy were explored via an international survey that TIF designed and distributed in 2020. As explained in detail in the relevant report, majority of respondents demonstrated a positive attitude towards gene therapy (66%). Moreover, respondents indicated that apart from the clinical aspects of thalassaemia, their social life, education, employment and finances also are affected thus suggesting a high burden of disease on the individual and their families. Finally, 35.7% of respondents who were patients indicated that they would choose to undergo gene therapy if they were eligible and 52.6% of respondents who were parents indicated that they would be positive for their children to undergo gene therapy.

Feedback on Draft Background and Scope Document:

The consequences of the disease are largely dependent on the quality of care received by patients and this impacts not only the health of the individual but also their ability to fully integrate into society both socially and professionally. Without treatment β-thalassaemia major (TDT) remains a lethal childhood disease while non-transfusion dependent thalassaemia (NTDT) is expected to present complications later in life, very often leading to transfusion dependency, and the possibility of premature death in many patients.

The patients who today endure daily iron chelation therapy, regular blood transfusions, frequent monitoring tests for secondary iron-related organ complications and are living with organ damage into their 50s are those patients who have and continue to benefit from the optimum quality care provided in expert centres by experienced healthcare providers, and are more often found in settings of adequate financial support and robust healthcare and public health infrastructures.

However, even these patients have also a quality of life price to bear. These represent a minority of the total thalassaemia patient population (even in developed countries). The greatest majority of living patients are surviving with suboptimal care either due to inadequate clinical support or due to poor adherence to lifelong treatment, or simply because health authorities have *other priorities*, notwithstanding the financial burden and strain that many families endure in their effort to cover out-of-pocket expenses for treatment and tests. The outlook for these patients is dire – many will live without a sustainable and acceptable quality of life, develop severe disabilities and ultimately die young.

The need for a permanent cure for their disease however is applicable to both groups of patients. For the former, a curative approach will *free* them from the myriad of uncertainties (e.g. blood sufficiency, organ complications etc) and struggles (e.g. organizing their personal and professional lives around hospital visits for blood transfusions, doctors' appointments across multiple disciplines for monitoring tests and consultations etc) that they experience daily. Still many from this group may not be eligible due to extensive organ damage that may not allow the safe application of myeloablation. It is indeed this requirement that

causes the toxicity of the whole treatment and issues such as infertility need to be considered. For the latter group, a curative option is a chance for life.
With these facts in mind there is a medical but more importantly a moral obligation to enable the accessibility and availability of gene therapy as a choice. Surviving with a lifelong disabilities is a price which both parents and their children can do without. This is not to even mention the wider public health benefits including relieving the burden on the healthcare system for ensuring continual access to safe and adequate supplies of blood through developing more resilience of blood transfusion services, provision of costly drugs that need to be taken daily for iron chelation therapy and many others.

The section on Outcomes is a good synopsis of the 'harms' that accompany this condition. However, it is a list which does not convey the feelings of child with deformity (due to poor a transfusion regimen in early life), or to an adolescent who has to face his/her peers without secondary sexual development, or to the student who has to sit exams but has had to miss school because of clinic and transfusion times that conflict with school or university schedules, or the difficulty of employment for the same reason. Above all it fails to convey the feelings that an uncertain future brings. Patients with good social support have developed adequate coping mechanisms and adapt as best they can to impositions of their condition. However, this should not be a reason to deprive them of a choice for a cure.

Finally, we wish also to congratulate ICER for its intention to develop a de novo analytic model to assess lifetime cost effectiveness, with consideration to quality of life aspects. This is an objective approach which however is only one tool in assessing a healthcare need. We commend your intention to involve patients in this assessment and we place at your disposal the cost-of-illness model that has been developed by our Federation to assess costs based on the treatment and monitoring needs – the model is available upon request at thalassaemia@cytanet.com.cy.

The Thalassaemia International Federation, remains fully committed to continuing its efforts to enable the accessibility of gene therapy for thalassaemia patients as a choice and therefore supports ICER's efforts towards providing a complete report on the value of betibeglogene autotemcel for beta thalassaemia, realizing its ultimate value for the patients.

On behalf of the Board of Directors of Thalassaemia International Federation (TIF),

Panos Englezos
President

Dr Androulla Eleftheriou
TIF Executive Director

Dr Michael Angastiniotis
TIF Medical Advisor