



January 27, 2020

**Beta Thalassemia Review Team**

Institute for Clinical and Economic Review (ICER)  
Two Liberty Square, 9<sup>th</sup> Floor  
Boston, MA 02109

**RE: bluebird bio's response to the proposed scope for ICER's value assessment of transfusion-dependent beta thalassemia therapies**

Dear ICER Review Team:

bluebird bio appreciates the opportunity to participate in ICER's evaluation of LentiGlobin<sup>®</sup> for the treatment of transfusion-dependent  $\beta$ -thalassemia (TDT). bluebird bio is pleased to submit feedback on this review's draft background and scope document that was published on January 6<sup>th</sup>, 2020. bluebird bio offers recommendations with the belief that these recommendations will ensure this review to be more accurate and meaningful 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. Combination chelation therapy is an important component of an analysis.
2. LentiGlobin and luspatercept (Reblozyl<sup>®</sup>) should be compared to one another in the economic evaluation.
3. A microsimulation modeling approach should be undertaken for this economic evaluation rather than a Markov approach.
4. Avoid analyses that use short term time-horizons when evaluating the cost-effectiveness of LentiGlobin.
5. An outcomes-based payment structure should be used for LentiGlobin when evaluating its value.

**1. Combination chelation therapy is an important component of an analysis**

As noted in the draft scoping, combination chelation therapy may be indicated for severe iron overload. Real-world evidence provided to ICER by bluebird (see ISPOR 2018 poster on US TDT treatment patterns and costs of care<sup>1</sup>) indicates that approximately 20% of TDT patients have utilized some form of combination (oral/injection) chelation therapy. Published economic models in TDT<sup>2</sup> have utilized different utility values for the oral versus injection chelation health state, so it will be important for ICER to consider the impact of combination chelation on both costs and quality of life in the economic model for LentiGlobin for TDT.



## **2. LentiGlobin and luspatercept should be compared to one another in the economic evaluation.**

The draft scoping document indicates that LentiGlobin will not be directly compared with luspatercept in the economic evaluation. bluebird bio firmly believes that ICER should evaluate the clinical and cost-effectiveness of LentiGlobin compared to luspatercept in its review, in addition to comparing LentiGlobin to current standard of care. If approved by the FDA, LentiGlobin will be a new treatment option for TDT, similar to luspatercept, which was recently approved for the treatment of TDT in the US.<sup>3</sup> Because some patients, clinicians, and payers will be faced with a decision to choose between the two treatments, we believe it is appropriate that the economic evaluation compare the treatments to one another. Having this information will contribute to better informed decision-making by these stakeholders.

## **3. A microsimulation modeling approach should be undertaken for this economic evaluation rather than a Markov approach.**

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.<sup>4</sup> 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.

## **4. Avoid analyses that use short term time-horizons when evaluating the cost-effectiveness of LentiGlobin.**

Patients with TDT require life-long blood transfusions as well as accompanying iron chelation therapy to address iron overload.<sup>5</sup> 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.<sup>4</sup> 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.<sup>1,6</sup>

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.

**5. An outcomes-based payment structure should be used for LentiGlobin when evaluating its value.**

bluebird bio firmly believes in the potential value of the life-long transformative benefits that LentiGlobin can offer to TDT patients, their caregivers, physicians and the entire health system. Our goal is to share with US payers the risk of uncertainty associated with LentiGlobin's expected long-term clinical benefit by utilizing an outcomes-based payment approach for LentiGlobin, as is being done in the European Union. With such a proposed model, payments would be made over a five-year period from the time of LentiGlobin infusion. After the initial payment around the time of infusion, subsequent payments are contingent upon patients achieving outcome milestones. bluebird bio would share 80% of the economic burden associated with the risk of LentiGlobin treatment being unsuccessful in an individual patient. Our commitment is to make LentiGlobin affordable to patients and health systems across geographies we serve. We therefore propose that ICER's model adopts an outcomes-based payment schedule spread over five years starting at infusion with LentiGlobin.

bluebird bio once again appreciates the opportunity to share feedback with ICER on this review's draft scope. Please feel free to contact us should you wish to discuss any of the above recommendations in further detail.

Kind regards,

Clark Paramore

Head of Value Demonstration



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*b colorful, b cooperative, b yourself*

## References

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6. Paramore, C., Helfer, J., Levine, L., Kousoulakou, H., Larkin, M. Patient-reported burden of transfusion-dependent  $\beta$ -thalassemia in the USA and the UK measured using a digital app. *ISPOR Europe*. 2019.

January 27, 2020

Re: ICER Open Input Submission

At Bristol-Myers Squibb Company (BMS), we appreciate the opportunity to respond to the ICER and New England CEPAC call for open input for luspatercept and luspatcept for the treatment of beta thalassemia. The lists of relevant publications and stakeholders are provided below.

### **1. Luspatercept peer-reviewed publications**

The following is the list of 27 publications (1-27) on luspatercept or beta-thalassemia. The manuscript for BELIEVE trial is currently being submitted to a journal for publication.

1. Piga A, Melpignano A, Perrotta S, Borgna-Pignatti C, Caruso V, Voskaridou E, et al. ACE-536 increases hemoglobin levels in adults with betathalassemia: Preliminary results from a phase 2 study. *Haematologica*. 2014;99:230-1.
2. Piga AG, Perrotta S, Melpignano A, Borgna-Pignatti C, Voskaridou E, Caruso V, et al. ACE-536 increases hemoglobin and decreases transfusion burden and serum ferritin in adults with beta-thalassemia: Preliminary results from a phase 2 study. *Blood*. 2014;124(21).
3. Piga A, Perrotta S, Borgna-Pignatti C, Gamberini MR, Melpignano A, Voskaridou E, et al. Luspatercept (ACE-536) increases hemoglobin and decreases transfusion burden and liver iron concentration in adults with beta-thalassemia: Preliminary results from a phase 2 study. *Haematologica*. 2015;100:17.
4. Piga A, Perrotta S, Gamberini MR, Voskaridou E, Melpignano A, Filosa A, et al. Luspatercept (ACE-536) reduces disease burden, including anemia, iron overload, and leg ulcers, in adults with beta-thalassemia: Results from a phase 2 study. *Blood*. 2015;126(23):752.
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11. Piga A, Tartaglione I, Gamberini R, Voskaridou E, Melpignano A, Ricchi P, et al. Luspatercept increases hemoglobin and decreases transfusion burden in adults with B-thalassemia. *Haematologica*. 2017;102:15-6.



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12. Piga AG, Perrotta S, Melpignano A, Borgna-Pignatti C, Gamberini MR, Voskaridou E, et al. Luspatercept decreases transfusion burden and liver iron concentration in regularly transfused adults with  $\beta$ -thalassaemia. *Haematologica*. 2017;102:89-90.
13. Piga AG, Perrotta S, Melpignano A, Borgna-Pignatti C, Gamberini MR, Voskaridou E, et al. Luspatercept increases haemoglobin and improves quality of life in non-transfusion dependent adults with  $\beta$ -thalassaemia. *Haematologica*. 2017;102:90.
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18. Piga A, Perrotta S, Gamberini MR, Voskaridou E, Melpignano A, Filosa A, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with b-thalassemia. *Blood*. 2019;133(12):1279-89.
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22. Viprakasit V, Taher A, Hermine O, Porter J, Piga A, Kuo KHM, et al. Evaluating luspatercept responders in the phase 3, randomized, double-blind, placebo-controlled believe trial of luspatercept in adult beta-thalassemia patients (pts) who require regular red blood cell (RBC) transfusions. *Blood*. 2019;134.
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## 2. List of Principal Investigators

Name	Country	Trials
Antonio Piga	Italy	<ul style="list-style-type: none"> <li>○ A536-04 Ph2 Study to Evaluate the Effects of ACE-536 in Patients With Beta-thalassemia and A536-06 Beta-thalassemia extension study</li> <li>○ ACE-536-B-THAL-004 Study of Safety &amp; PK of Luspatercept in Pediatric Subjects Who Require Regular RBC Transfusions Due to <math>\beta</math>-Thalassemia</li> </ul>
Maria-Domenica Cappellini	Italy	<ul style="list-style-type: none"> <li>○ ACE-536-B-THAL-001 An Efficacy and Safety Study of Luspatercept Vs Placebo in Adults Who Require Regular Red Blood Cell Transfusions Due to <math>\beta</math> Thalassemia (BELIEVE)</li> </ul>
Ali Taher	Lebanon	<ul style="list-style-type: none"> <li>○ ACE-536-B-THAL-003 To Document the Burden of Illness on the Quality of Life and the Impact on Healthcare Utilization in <math>\beta</math>-thalassemia Subjects Who Are Transfusion Dependent and Non-transfusion Dependent Receiving Standard of Care</li> <li>○ ACE-536-B-THAL-002 A Study to Determine the Efficacy and Safety of Luspatercept in Adults With Non Transfusion Dependent <math>\beta</math>-Thalassemia (BEYOND)</li> </ul>

## 3. Key Opinion Leaders

Name	Country	Organization	Link
Alexis Thompson	USA	<ul style="list-style-type: none"> <li>○ Ann and Robert H. Lurie Children's Hospital of Chicago in Chicago, Illinois</li> <li>○ Northwestern University Feinberg School of Medicine</li> </ul>	<a href="https://www.cancer.northwestern.edu/find-a-physician/profile.html?xid=13545">https://www.cancer.northwestern.edu/find-a-physician/profile.html?xid=13545</a>
Sujit Sheth	USA	<ul style="list-style-type: none"> <li>○ Cornell Medical College</li> </ul>	<a href="http://vivo.med.cornell.edu/display/cwid-shethsu">http://vivo.med.cornell.edu/display/cwid-shethsu</a>
Thomas Coates	USA	<ul style="list-style-type: none"> <li>○ Children's Hospital of Los Angeles</li> </ul>	<a href="https://keck.usc.edu/faculty-search/thomas-d-coates/">https://keck.usc.edu/faculty-search/thomas-d-coates/</a>

January 27, 2020

Re: ICER Open Input Submission

At Bristol-Myers Squibb Company (BMS), we appreciate the opportunity to respond to the ICER and New England CEPAC call for comments for draft scoping document for the assessment of luspatercept and lusparcept for the treatment of beta thalassemia. Our recommendations for the development of the scoping document are summarized below.

### **1. Luspatercept is a major advancement for a rare disease lacking innovation**

$\beta$ -thalassemia is a rare, life-long congenital blood disease caused by a genetic deficiency that leads to ineffective erythropoiesis and severe anemia. There have been limited advances in treatments for  $\beta$ -thalassemia, primarily restricted to iron chelating agents, leaving sub-optimal options for the management of the disease. Luspatercept is the first and only erythroid maturation agent (1). Luspatercept's unique mechanism of action addresses the underlying ineffective erythropoiesis in  $\beta$ -thalassemia to improve anemia and reduce red blood cell (RBC) transfusion burden.

### **2. Analytical framework should include transfusion burden as a measure of key clinical benefit**

Luspatercept was evaluated in the phase 3, multicenter, randomized, double-blind, placebo-controlled BELIEVE trial of 336 adult patients with  $\beta$ -thalassemia requiring regular RBC transfusions (2). The primary endpoint of the BELIEVE trial was the proportion of patients achieving RBC transfusion burden reduction ( $\geq 33\%$  reduction from baseline) with a reduction of at least 2 units during a pre-specified time period (week 13 to week 24 of the study) (2, 3). ICER's analytical framework for review and cost-effectiveness analysis should include transfusion burden reduction as a key measure of clinical benefit. Transfusion burden directly reflects the amount of iron intake into body. Since the body lacks an efficient mechanism to excrete the excess iron, regular transfusions can lead to iron overload, development of related complications, and negative impacts on long-term prognosis.

### **3. ICER's stakeholder input for cost and concerns regarding novel treatments**

The background section of the scoping documents mentions that patients are optimistic about the improvements in hemoglobin, although they have concerns regarding its cost and the durability of luspatercept's effect. ICER should provide source (citation) for this statement. The background section does not mention concerns regarding cost of gene therapy, which can cost more than \$2 million, and has been the subject of several recent publications (4-7). Additionally, some clinical experts have raised concerns about the conditioning regimen for gene therapy or hematopoietic stem cell transplantation (HSCT) which carries risks of both early transplant-associated toxicity as well as late effects like infertility and secondary malignancies (8-14).

### **4. Change in hemoglobin (Hgb) would not reflect a clinical benefit because the trial was designed to maintain a steady pre-transfusion Hgb level**

The scoping document mentions change in Hgb level as one of the outcome measures. Luspatercept's clinical trial was designed to maintain pre-transfusion target hemoglobin levels while simultaneously reducing RBC transfusion burden. Hence, this outcome would not reflect a measure of efficacy of





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luspatercept in this setting. Improvements in hemoglobin with luspatercept are being assessed in the non-transfusion-dependent population in an ongoing Phase 2 study (15).

**5. Health states for the cost-effectiveness model should include different levels of transfusion burden**

The scoping document mentions that the model will consist of health states including alive and transfusion dependent, alive and transfusion independent, and dead. This model structure could be limited in capturing the full economic value of luspatercept. The model should also include health states based on the transfusion burden (low, medium and high) because some patients will transition from high burden to medium and then to low burden.

BMS is taking this opportunity to comment on the draft scoping document because of the importance that our company places on maintaining an innovation ecosystem to discover, develop and deliver transformational treatments for patients in the US and globally. BMS outlined a number of areas in the scoping document, if improved, could strengthen ICER's methodology and approach. We hope that ICER incorporates these recommendations into the final scoping document.

Sincerely,

A handwritten signature in cursive script that reads "M. K. Higashi".

Mitch K. Higashi, PhD

Head of US Medical Health Economics and Outcomes Research

## References

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