15 December 2022

Emerging Gene Therapies for Sickle Cell Disease Review Team
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800, Boston, MA 02108

RE: bluebird bio's Response to ICER's Draft Scoping Document on Emerging Gene Therapies for Sickle Cell Disease

Dear ICER Review Team:

On behalf of bluebird bio, the manufacturer of lovotibeglogene autotemcel (lovo-cel), an investigational gene therapy for sickle cell disease (SCD), we thank ICER for the opportunity to respond to the Draft Scoping Document for the evaluation of gene therapies for SCD.

The SCD community has been underserved and marginalized for decades, and progress to improve care, treatments, and outcomes has been dismally slow compared with other disease areas. As ICER undertakes its review, we encourage you to not only listen to feedback from patients and caregivers, but to act on and incorporate it. Doing so will ensure the assessment reflects the full impact that lovo-cel is expected to have on health and economic outcomes in patients with severe SCD, their caregivers and families, and in the broader society. Below are recommendations from bluebird bio to that end.

Comment 1:	ICER's assumption regarding the durability of a one-time gene therapy should reflect the treatment mechanism of action, which is expected to be lifelong, and the totality of available clinical evidence.
Comment 2:	ICER's cost-effectiveness analysis should use a societal perspective as a co–base-case analysis.
Comment 3:	ICER's economic model should use appropriate costing data from patients with severe SCD to align with the subset of patients included in the scope of this appraisal.
Comment 4:	ICER should be mindful of the challenges and limitations associated with its previous SCD model structure.

Comment 1: ICER's assumption regarding the durability of a one-time gene therapy should reflect the treatment mechanism of action, which is expected to be lifelong, and the totality of available clinical evidence.

Gene therapy with lovo-cel consists of autologous transplantation of hematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding a modified form of the βA-T87Q-globin gene. Once patients have the modified gene, their red blood cells can produce antisickling hemoglobin, HbAT87Q, which in turn decreases the proportion of abnormal sickle hemoglobin (HbS), sickled red blood cells, hemolysis, and other complications of SCD. Additionally, because lovo-cel is a modified HbAT87Q with antisickling properties, any residual HbS produced is less able to sickle, further decreasing the untoward effects of HbS. Lovo-cel is infused as a one-time cellular therapy. After infusion of lovo-cel, gene-modified hematopoietic stem cells are expected to undergo self-renewal and transfer a healthy copy of the βA-T87Q-globin gene to daughter blood cells for the lifetime of the patient. This mechanism of expression of the βA-T87Q-globin gene and production of HbAT87Q provide an expected lifetime of

durable clinical benefits. Clinical data observed to date do not suggest otherwise.

Therefore, ICER's base-case analysis for estimating lovo-cel's cost-effectiveness should assume the level of clinical benefit will remain durable for the lifetime of the modeled patients to reflect lovo-cel's mechanism of action accurately.

Comment 2: ICER's cost-effectiveness analysis should use a societal perspective as a co−base-case analysis.

Based on published evidence that societal costs of SCD are substantial relative to direct healthcare costs, ICER should use a societal economic analysis, incorporating not only work productivity but also time lost to informal care and unpaid work, as well as lost earnings due to foregone educational attainment as a co−base-case analysis.

Patients with SCD and their caregivers are significantly affected in their employment, academic pursuits, work productivity, and career growth. In a study of patients from an SCD clinic in the United States (US), although the population studied appeared to be less severe than those in the HGB-206 study (e.g., only 44.8% with the SS genotype, and some without any pain event in the past year), only 30% of respondents reported being employed, and approximately 65% reported having given up a job due to SCD (Holdford et al., 2021). Of those employed, the average annual cost of absenteeism and presenteeism per person due to pain events was estimated to be $15,103. Furthermore, three-fourths of respondents reported difficulty in completing essential daily tasks, such as childcare, housework, and grocery shopping. Annual losses in unpaid work were estimated to be $21,547 per patient and $19,662 per caregiver. The authors estimated the total indirect costs due to absenteeism, presenteeism, and lost productivity in unpaid work to exceed previously published estimates of direct medical costs in a similar population, confirming the importance of incorporating indirect costs in this population.

Substantial impacts of SCD on patients' lifetime earnings are estimated in another recently published study by Graf and colleagues (2022). The authors estimated that a potential cure for SCD would increase the median annual earnings of patients with SCD, most of whom are Black, from $25,442 to $38,618, compared with the $45,438 median income of the matched controls. This equates to additional lifetime earnings of $1.3 million per patient. In addition to the indirect costs due to lost work productivity accounted for in the Holford study (2021), Graf and colleagues (2022) discussed the impact of SCD on patients' educational attainment as a contribution to the estimated earning gaps.

Comment 3: ICER's economic model should use appropriate costing data from patients with severe SCD to align with the subset of patients included in the scope of this appraisal.

SCD is a lifelong disorder of heterogeneous expression, where the economic burden varies significantly by disease severity (Gallagher et al., 2022). We recommend ICER carefully evaluate studies on SCD costs to ensure ICER's economic model incorporates costs for patients with severe SCD, who are the focus of ongoing trials for gene therapies reviewed in this ICER assessment.

In the Gallagher and colleagues analysis (2022), claims data for patients with severe SCD revealed that nearly 80% of insured patients were covered by Medicaid plans, and the economic burden of SCD was estimated to be substantially higher in this Medicaid population than in the commercially insured population. Furthermore, when the same study analyzed healthcare resource use and direct costs of SCD by age group, resource utilization and costs increased substantially as patients in the Medicaid population aged. For example, the 5-year costs of inpatient care alone increased from less than $200,000 in those younger than 18 years to nearly $600,000 in those 18 to 30 years.

Based on these observations, we urge ICER's economic modeling team to identify direct costs of SCD from studies of Medicaid populations with severe presentation of SCD. In addition to the Gallagher study (2022), we recommend that ICER review studies by Shah and colleagues (2020), Campbell and colleagues (2020), and a systematic review of published US-based economic analyses in patients with SCD by Baldwin and colleagues (2022).

Comment 4: ICER should be mindful of the challenges and limitations associated with its previous SCD model structure.

ICER's cost-effectiveness model structure for the current evaluation was not presented in the Draft Scoping Document. If the review team plans to use a structure similar to the Markov-based model designed for the ICER SCD assessment in 2020 (ICER, 2021), we have concerns about the model's ability to incorporate all critical health consequences without sacrificing transparency. In ICER's 2020 model, despite a simple model structure diagram in the report, the overlap among acute and chronic conditions paired with the role of patient history in subsequent events (e.g., 3 or more pain crises in the past year) suggest an unmanageable number of health states for a cohort-based, state-transition modeling approach. Additionally, a cohort-based, state-transition model is limited in its ability to reflect the heterogeneity that is observed among patients with SCD. For these reasons, and in alignment with good modeling practice guidelines from ISPOR (Siebert et al., 2012), we believe a patient-level simulation modeling approach is more appropriate to capture the complexity of the disease states and the heterogeneity of the population (Purser et al., 2020; Johnson et al., 2022).

Gene therapy represents a tremendous opportunity to transform the lives of individuals living with SCD and their families. We appreciate that ICER recognizes the significance of these therapeutic advancements and its obligation to capture the full value these treatments are poised to deliver for this community. We look forward to a continued dialogue throughout this review. If you have any questions, please contact Meghan Gallagher.

Sincerely,

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December 15, 2022

Dear ICER Review Team,

Vertex Pharmaceuticals Incorporated appreciates the opportunity to participate in ICER's evaluation of its investigational product, exagamglogene autotemcel (exa-cel) for the treatment of sickle cell disease (SCD). Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases. Our goal is to create new possibilities in medicine to cure diseases and improve lives. As ICER knows, gene therapies hold enormous potential to treat otherwise intractable and often life-threatening medical conditions for which conventional treatments either do not exist or have proven deeply inadequate, like SCD. We provide the following recommendations and clarifications to the draft scoping document for the review of Emerging Gene Therapies for SCD:

Clarification on the role of fetal hemoglobin (HbF) and further description of exa-cel's MOA

Fetal hemoglobin (HbF) was introduced in the ICER draft scoping document as a modifier of disease severity; below we provide additional information on the role of HbF, and hereditary persistence of HbF (HPFH), as important to the mechanism of action (MOA) of exa-cel.

HbF is the predominant hemoglobin type prior to birth and during the newborn period. In individuals who do not have SCD, HbF production is reduced and is almost completely replaced by adult hemoglobin (HbA) in the first six to 12 months after birth. The onset of symptoms in SCD typically occurs several months after birth when hemoglobin S (HbS) rather than HbA becomes predominant, due to the inclusion of the disease-causing mutated β-globin gene in the hemoglobin molecule[1,2]. Polymerization of HbS results in the characteristic sickling of red blood cells. HPFH is a condition in which HbF production does not stop in early childhood and instead continues in later life[3]. The continued production of HbF can have a protective effect by inhibiting polymerization of Hb when it is also expressed in a sufficient number of cells[2].

Studies have shown patients with SCD and HPFH (with approximately 30% HbF expression) have a benign clinical course of SCD[4]. Even when sickle hemoglobin concentrations are >60%, case reports show patients have few or no symptoms of SCD[4]. Clinically, higher HbF levels have been shown to ameliorate symptoms such as vaso-occlusive crises (VOCs), leg ulcers, osteonecrosis, and acute chest syndrome (ACS)[5].

The manufacturing of exa-cel relies on non-viral, *ex-vivo* CRISPR/Cas9 gene editing[6]. CRISPR/Cas9 mediated gene editing only occurs at the erythroid lineage-specific enhancer region of the *BCL11A* gene using a specific single-guide RNA and Cas9 nuclease, thereby conferring lineage specificity and avoiding pleiotropic effects[6]. The goal of this genetic modification is to reactivate the expression of γ-globin mRNA in erythroid precursors, which results in an increase in HbF protein levels in adult erythroid cells. In preclinical studies, on-target allelic editing was confirmed and there was no evidence of off-target editing[6].

Recommendation to include regulatory approved and ICER-assessed non-curative therapies as comparators for exa-cel

Regulatory approved and ICER-assessed[7] non-curative therapies (e.g., voxelotor and crizanlizumab) are appropriate comparators for exa-cel. These therapies should be considered as comparators in the evaluation of any new SCD treatment, and particularly any gene therapies that have the potential to ameliorate the need for these standard treatments. Failure to include these recently approved therapies will also result in underestimation of the current cost of care of SCD in the US.

Confirmation of the appropriateness of a cohort-level decision-analytic model framework and recommendation for a modified societal perspective to be utilized as a co-base case

The draft scoping document noted that the model structure will be based upon previously published models of SCD, e.g., previous ICER SCD assessment[7] and economic model of a hypothetical gene therapy in SCD[8]. We consider a cohort-level decision-analytic model framework similar to these previous publications is appropriate for this economic evaluation.

We also recommend a modified societal perspective as a co-base case. The comprehensive impact of SCD has been recognized by ICER and others, which was highlighted in ICER's previous assessment of recently approved non-curative therapies[7]. ICER and the Sick Cells survey found significant unemployment and work, productivity, and activity impairment in patients with SCD or their caregivers[7] and we are aware of additional data sources that we can provide to inform model inputs for the societal perspective[9]. The specific thresholds mentioned in the draft scoping document to qualify the modified societal perspective do not fully account for the significant impacts of SCD on patients and caregivers.

In addition, given that both crizanlizumab and voxelotor, two non-curative therapies that do not eliminate VOCs, as well as ICER's recent assessment in transfusion-dependent beta-thalassemia (TDT)[10] were able to reach the ICER-determined threshold for modified societal perspective as the co-base case, an assessment of a potentially curative therapy in SCD should incorporate the modified societal perspective as a co-base case.

Based on the MOA and clinical trial data to date, lifelong durability should be applied for exa-cel in the economic evaluation

Exa-cel is a gene edited hematopoietic stem cell (HSC)-based therapy and there is no known mechanism for HSC DNA to convert back to a wild-type sequence following CRISPR/Cas9 editing. In interim trial data presented on patients with SCD treated with exa-cel, at month six, the mean proportion of edited *BCL11A* alleles in bone marrow CD34+ hematopoietic stem and progenitor cells (HSPCs) and peripheral blood mononuclear cells was 86.6% and 76.0% respectively[11]. All 31 patients were VOC-free after infusion (duration from 2.0 to 32.3 months)[12]. Based on the MOA and clinical trial data to date, we recommend a base-case assumption of life-long durability for exa-cel in the economic evaluation.

A lifetime horizon is most appropriate when evaluating one-time potentially curative therapies and should be utilized for base-case and all scenario analyses in this review

The draft scoping document noted that cost-effectiveness will be estimated for time horizons shorter than lifetime. However, given the nature of the treatments under evaluation (one-time curative therapies), only a lifetime time horizon can fully capture the benefits of such therapies and is therefore the only appropriate time horizon to consider. The benefits of one-time gene therapies are to ameliorate a life-long disease indefinitely and it is expected that the clinical and economic benefits will materialize over the patient's lifetime, as described above in exa-cel's MOA and the anticipated permanence of gene editing. Utilizing only a lifetime time horizon is in alignment with other ICER assessments for one-time gene therapies[13].

Clarification on clinical trial design

ICER has defined the population of focus as patients with SCD and four VOCs over two years. However, patients in the exa-cel clinical trial were required to have a history of at least two severe VOCs per year for the previous two years prior to enrollment. Severe VOCs were defined as an acute pain event requiring a visit to a medical facility and administration of pain medications or RBC transfusions; ACS; priapism; or splenic sequestration[7]. This is a stricter definition than having a minimum of four VOCs in the prior two years as described in the current draft scoping document.

In addition, the draft scoping document noted that ICER intends to compare exa-cel and lovotibeglogene autotemcel (lovo-cel) to each other, data permitting. Notable differences in trial design must be considered when conducting such comparisons; particularly in the areas of clinical trial inclusion criterion and endpoint definitions[14,15].

Additional information on the impact of health disparities on the SCD patient population

We share the goal of reducing healthcare inequities, and support including this as a consideration in the ICER assessment. New data have confirmed this is a particularly important issue for patients with SCD, where a recent survey of 142 adults living with SCD showed most participants reported feeling that they had been treated unfairly while seeking their care and attributed it to their race (67%) and/or requesting more pain medicine (65%)[9]. This exemplifies barriers to care as reported in this patient population.

Recommendation to include a comprehensive set of SCD complications in the model to fully capture disease impact

We appreciate ICER's acknowledgement of the multisystem nature of SCD and the impact in nearly every organ in the body. Published literature have described the impact of SCD on multiple systems[16,17]. ICER's previous SCD assessment[7] noted many multisystemic acute and chronic complications, many of which are not included in the current list of complications in the draft scope. We recommend including the following additional complications: pulmonary embolism, acute infections, leg ulcers, and liver complications, which would ensure that the economic model holistically captures the impact of organ complications.

Sincerely,

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