



**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Office of Biostatistics and Pharmacovigilance (OBPV)  
Division of Pharmacovigilance (DPV)**

**PHARMACOVIGILANCE PLAN REVIEW FOR ORIGINAL BLA MEMORANDUM**

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**To:** Graeme Price, PhD  
Chair of the Review Committee  
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**Through:** Kerry Welsh, MD, PhD  
Branch Chief, PB3

Meghna Alimchandani, MD  
Deputy Director DPV  
OBPV, CBER, FDA

**Subject:** Review of Pharmacovigilance Plan

**Sponsor:** bluebird bio, Inc.

**Product:** lovotibeglogene autotemcel (autologous  
hematopoietic stem cell-based gene therapy)

**Application Type / Number** BLA / STN 125788/0

**Proposed Indication** Treatment of patients 12 years of age or older with  
sickle cell disease and a history of vaso-occlusive  
events.

**Submission Date:** April 21, 2023

**Action Due Date:** December 20, 2023

## **1 OBJECTIVE**

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under original BLA 125788/0 based on the safety profile of lovotibeglogene autotemcel (also referred to as lovo-cel or Lyfgenia throughout this memo). Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for lovotibeglogene autotemcel, should the indication for this product be approved. Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

## **2 BACKGROUND**

Sickle cell disease (SCD) is a group of autosomal-recessive genetic disorders that are caused by mutations in the  $\beta$ -globin gene<sup>1</sup> which results in the production of sickle hemoglobin (HbS) which is less soluble than normal fetal or adult hemoglobin.<sup>2</sup> Under low oxygen conditions, red blood cells containing the HbS develop a rigid C-shaped configuration (i.e., sickle) which impedes their flow through small blood vessels and causes the red blood cells to die early.<sup>3</sup> Signs and symptoms of SCD begin early in life and the disease leads to various acute and chronic complications, including acute chest syndrome, pain crises due to vaso-occlusive episodes (VOEs), anemia, avascular necrosis of bone tissue, thrombosis, hand-foot syndrome (painful swelling in hands and feet), infections, and organ damage.<sup>4</sup>

Millions of people worldwide are affected by SCD, especially individuals whose ancestors came from sub-Saharan Africa, South America, the Caribbean, Central America, India, the Middle East, and Mediterranean countries.<sup>5</sup> In the U.S., approximately 100,000 individuals are affected by SCD, including approximately 1 out of every 365 births among Black individuals and 1 out of every 16,300 births among Hispanic individuals.<sup>5</sup>

Treatment with lovo-cel is intended to add functional copies of a modified  $\beta$ -globin gene into patients' hematopoietic stem cells (HSCs) through ex-vivo transduction of autologous CD34+ cells using a lentiviral vector (LVV). After product infusion, the transduced CD34+ HSCs engraft in the bone marrow and then differentiate to produce red blood cells with functional hemoglobin similar to wild-type hemoglobin. The goal of lovo-cel gene therapy is to prevent the occurrence of VOEs and reduce hemolytic anemia events by reducing the concentration of HbS and preventing red blood cell sickling during hypoxic conditions. Gene therapy is intended to reduce tissue injury, alleviate pain crises, and prevent progression of systemic disease caused by sickled red blood cells. Lovo-cel is not expected to reverse established SCD-related pathology.

### 3 PRODUCT INFORMATION

#### 3.1 Product Description

Per the sponsor's draft U.S. Package Insert (USPI) Section 11, "Lovotibeglogene autotemcel is a  $\beta^{A-T87Q}$ -globin gene therapy consisting of autologous CD34+ cells from patients with sickle cell disease containing hematopoietic stem cells (HSCs) transduced with BB305 LVV encoding  $\beta^{A-T87Q}$ -globin, suspended in cryopreservation solution. LYFGENIA is intended for one-time administration to add functional copies of a modified form of the  $\beta$ -globin gene ( $\beta^{A-T87Q}$ -globin gene) into the patient's own HSCs." The product is supplied in patient-specific infusion bag(s) that contain a frozen suspension of genetically modified autologous cells and is thawed prior to intravenous (IV) administration. The product contains 5% dimethyl sulfoxide (DMSO).

*Reviewer comment: The sponsor's Summary of Clinical Safety (SCS) indicates that BB305 LVV drives high levels of gene expression but only in the erythroid lineage. The sponsor's draft USPI indicates that DMSO may cause hypersensitivity reactions, including anaphylaxis.*

#### 3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to original BLA 125788/0 is as follows: "Lyfgenia is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events." OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

### 4 PERTINENT REGULATORY HISTORY

This is an original BLA submission, and no patients have been treated with lovo-cel in the post-market/commercial setting. However, there are two approved gene therapy products manufactured by the same sponsor, with potential relevance for considering the safety profile of lovo-cel for pharmacovigilance (PV) purposes: beti-cel (Zynteglo; STN 125717) which is for the treatment of transfusion dependent beta thalassemia (TDT) and eli-cel (Skysona; STN 125755) which is for the treatment of congenital adrenoleukodystrophy (CALD). Both of these products use a lentiviral-based vector and are manufactured by bluebird bio.

The sponsor provided an overview comparing vector-related safety results for lovo-cel, beti-cel, and eli-cel. Among individuals treated with eli-cel (n=67), 3 (4.5%) individuals experienced 3 insertional oncogenesis events and "developed a hematologic malignancy (myelodysplastic syndrome, MDS) associated with gene expression changes in known proto-oncogenes (*MECOM* or *PRDM16*) containing a Lenti-D LVV IS" (IS=integration site). The sponsor noted that the Lenti-D LVV used in eli-cel uses a constitutively active ubiquitous MNDU3 promoter which is different from the erythroid-specific promoter that is used in the manufacturing of lovo-cel and beti-cel. The sponsor

reported that no insertional oncogenesis events occurred in individuals who received lovo-cel (n=50) or beti-cel (n=63).

Persistent oligoclonality occurred in 3 (6.1%) participants who received lovo-cel, 2 (3.2%) participants who received beti-cel, and 17 (27.0%) participants who received eli-cel. The sponsor noted that the differences in persistent oligoclonality between products is “likely due to differences in manufacturing processes and promoters used between the different LVVs.” No confirmed vector-related replication-competent lentivirus (RCL) was detected in participants following receipt of lovo-cel, beti-cel, or eli-cel.

## 5 DESCRIPTION OF LOVOTIBEGLOGENE AUTOTEMCEL CLINICAL TRIAL SAFETY DATABASE

### 5.1 Clinical studies

The clinical study safety data reviewed are from the sponsor’s SCS and Integrated Summary of Safety (ISS) submitted to BLA 125788/0. Table 1 provides an overview of the clinical studies supporting the safety of lovo-cel.

OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor’s data initially submitted to the BLA, to inform decisions pertaining to PV planning, should BLA 125788/0 be approved. Please refer to the package insert for the final clinical safety data.

**Table 1. Summary of clinical studies supporting the safety of Lovo-cel\***

Study Identifier (Status)	Study Title	Number of Subjects and Age Ranges	Drug Product Characteristics and Recommended Cell Dose	Interim Data Cut-off Date for Ongoing Studies
HGB-205 (completed 26 February 2019)	A Phase 1/2 Open Label Study Evaluating the Safety and Efficacy of Gene Therapy of the $\beta$ -Hemoglobinopathies (Sickle Cell Anemia and $\beta$ -Thalassemia Major) by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo	7 planned (SCD or TDT)  3 subjects with SCD were treated and completed the study (ages 13, 16, and 21 years)	Manufacturing Process 0  Autologous cell source: bone marrow harvest  Cell dose: $\geq 2.0 \times 10^6$ CD34+ cells/kg	NA; study complete

	with a Lentiviral $\beta^{A-T87Q}$ -globin Globin Vector (LentiGlobin BB305 Drug Product)			
HGB-206 (study ongoing; enrollment and treatment completed)	A Phase 1/2 Study Evaluating Gene Therapy by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with the LentiGlobin BB305 Lentiviral Vector in Subjects with Severe Sickle Cell Disease	Approximately 50 subjects $\geq 12$ and $\leq 50$ years of age with SCD planned  45 subjects treated (7 in Group A; 2 in Group B; 36 in Group C)  38 subjects completed	Manufacturing Process 1 (Group A and B), 2 (Group B), and 2a (Group C)  Autologous cell source: bone marrow harvest for Groups A and B; plerixafor-mobilized cells for Group C  Cell dose: $\geq 1.5 \times 10^6$ CD34+ cells/kg (Group A); $\geq 2.0 \times 10^6$ CD34+ cells/kg (Group B); $\geq 3.0 \times 10^6$ CD34+ cells/kg (Group C)	11 August 2022
HGB-210 (ongoing)	A Phase 3 Study Evaluating Gene Therapy by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with the BB305 Lentiviral Vector in Subjects with Sickle Cell Disease	Approximately 35 adults and pediatric subjects $\geq 2$ and $\leq 50$ years of age with SCD planned  2 subjects treated	Manufacturing Process 2a  Autologous cell source: plerixafor-mobilized cells  Cell dose: $\geq 3.0 \times 10^6$ CD34+ cells/kg	01 August 2022

		0 subjects completed		
LTF-307 (ongoing)	Long-term Follow-up of Subjects With Sickle Cell Disease Treated With Ex Vivo Gene Therapy Using Autologous Hematopoietic Stem Cells Transduced With a Lentiviral Vector	Dependent on the number of subjects completing (or discontinuing) each parent study  41 subjects enrolled  0 subjects completed	No investigational treatment is administered in this study.	18 August 2022

\*Adapted from Sponsor's Summary of Clinical Safety, Table 1, BLA 125788/0, Module 2.7.4

***Reviewer Comment:** The manufacturing process for lovo-cel was refined over time and there were also changes in how stem cells were harvested from participants (i.e., bone marrow harvest or apheresis of plerixafor-mobilized cells). Lovo-cel treatment is preceded by medical procedures/interventions including stem cell harvest and myeloablative conditioning; these procedures/interventions have their own risks independent from the drug product lovo-cel. In addition, the underlying condition of SCD has many acute and chronic complications. For purposes of this PV review memo, the review of AEs will focus on those considered potentially related to or of specific interest for lovo-cel (per the sponsor's submission).*

## 5.2 Adverse events

### 5.2.1 Clinical study HGB-205

Three individuals with SCD were treated in the Phase 1/2 study HGB-205 (one 13-year old Black male, one 16-year old Black female, and one 21-year old White female); this study was completed on February 26, 2019. Participants were followed for 2-years post-infusion in this study and then were eligible to enroll in study LTF-307 for long-term follow-up (LTFU; i.e., total of 15 years).

i) Most common Adverse Events (AEs): All three participants experienced the following AEs in the period between conditioning and neutrophil engraftment: alopecia, diarrhea, nausea, pyrexia, stomatitis, vomiting, anemia, neutropenia, and thrombocytopenia.

ii) Serious AEs (SAEs): All three participants experienced SAEs; per the sponsor, none were product-related. SAEs included procedural pain due to bone marrow harvest (n=2), VOs (n=2; sickle cell anemia with crisis or acute chest syndrome), and hepatic enzymes increased (n=2). In addition, the following SAEs were experienced by one participant each: cholestasis, Staphylococcal bacteremia, and presyncope.

iii) Deaths: There were no deaths in Study HGB-205 through 2-years of follow-up post-infusion.

iv) AEs of special interest (AESIs): The sponsor identified potential events of interest (EOIs) in the following categories: hematologic disorders, immune-related AEs (e.g., autoimmune disorders, graft versus host disease [GvHD], opportunistic infections, HIV), infections, malignancies, and neurologic disorders. EOIs were meant to “focus on events related to lovo-cel or unanticipated consequences of gene therapy in long-term follow-up.” Per the sponsor, there were no product-related AEs and no AEs of HIV infection, autoimmune disease (including GvHD), or malignancies. There was no clonal dominance found on integration site analyses (ISA) and no detection of vector-derived RCL.

### **5.2.2 Clinical study HGB-206**

Forty-five individuals received lovo-cel in the Phase 1/2 study HGB-206; the study is ongoing although enrollment and treatment have been completed (data lock point August 11, 2022). Participants are followed for 2-years post-infusion in this study and then are eligible to enroll in study LTF-307 for LTFU.

i) Most common AEs: Two non-serious infusion reactions (i.e., hot flush in subject 206-(b) (6) and diastolic blood pressure decreased in subject 206-(b) (6)), were assessed by the study investigator and sponsor as related to lovo-cel. The sponsor commented that the infusion reactions were self-limited and consistent with infusion-related symptoms associated with DMSO (cryoprotectant used in lovo-cel). There was also a non-serious event of febrile neutropenia (subject 206-(b) (6)) that began after busulfan conditioning (onset Day 10 with resolution on Day 16) which was assessed as related to lovo-cel by the study investigator but as not related to lovo-cel by the sponsor (i.e., likely related to busulfan).

ii) SAEs: Two SAEs of anemia were assessed by the sponsor as related or possibly-related to lovo-cel in two participants with concurrent  $\alpha$ -thalassemia trait. One participant (subject 206-(b) (6)) was reported to have transfusion-dependent anemia on Day 249 which was ongoing as of the data cut-off. This individual also had six SAEs and two non-serious AEs of chronic pain from Day 308 to Day 449 which were considered as possibly lovo-cel-related by the study investigator but considered as related to the underlying disease by the sponsor. The second participant (subject 206-(b) (6)) who experienced an SAE of anemia had event onset on Day 374 and the event was ongoing as of the data cut-off (sponsor assessed as possibly related to lovo-cel). This second individual also experienced neutropenia with onset on Day 373 and resolution on Day 411 post-infusion (sponsor assessed as unlikely related to lovo-cel). Both individuals with SAEs of anemia had bone marrow biopsies that “confirmed red cell dysplasia consistent with stress erythropoiesis in the setting of SCD.”

iii) Deaths: One 27-year old male participant (subject 206-(b) (6)) experienced sudden onset of shortness of breath and visual compromise approximately 20-months

post-lovo-cel infusion. He subsequently experienced a ventricular fibrillation cardiac arrest and resuscitation efforts were unsuccessful. An autopsy indicated the cause of death was cardiovascular disease with SCD and asthma as contributing factors. The death was not considered related to lovo-cel. In addition, two participants (subjects 206-(b) (6) and 206-(b) (6) from study HGB-206 experienced fatal outcomes following an acute myeloid leukemia (AML) diagnosis while enrolled in study LTF-307 (see section 6.2 of this memo). None of the three deaths were considered lovo-cel-related per the sponsor.

iv) AESIs: Two individuals with concurrent  $\alpha$ -thalassemia trait experienced lovo-cel-related SAEs of anemia (discussed in SAE section above). In addition, two individuals experienced AML with fatal outcomes (subjects 206-(b) (6) and 206-(b) (6); discussed further in section 6.2); neither malignancy was determined by the sponsor to be due to insertional oncogenesis. One of the participants with fatal AML (subject 206-(b) (6) also experienced an SAE of MDS. There were no reports of graft failure or acute/chronic GvHD, and no evidence of insertional oncogenesis per the sponsor. All participants showed initial polyclonal reconstitution by ISA; one participant (subject 206-(b) (6) showed persistent oligoclonality due to a clone with four IS between Months 18 and 24 (latest visit). The sponsor indicated that findings from ribonucleic acid sequencing in this participant do not support LVV-driven gene expression changes. No immune-related events, infections, or neurologic disorders were considered by the sponsor to be of interest.

*Reviewer comment: Please see section 7 of this memo for details of the Pharmacovigilance Plan (PVP) which identifies hematologic malignancies as an important identified risk and insertional oncogenesis as an important potential risk.*

### **5.2.3 Clinical study HGB-210**

Two individuals have been treated with lovo-cel in the ongoing Phase 3 study HGB-210 (data lock point August 1, 2022).

i) Most common AEs: One participant (subject 210-(b) (6) experienced a non-serious product-related AE of increased gamma-glutamyl transferase (GGT) on Day 178 in conjunction with mild increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) (assessed as related to lovo-cel by study investigator but as not-related by sponsor).

ii) SAEs: No SAEs were considered related to lovo-cel per the sponsor. One participant (subject 210-(b) (6) experienced SAEs of febrile neutropenia and Staphylococcal infection (attributed by the investigator to conditioning), Staphylococcal sepsis (attributed to study procedure), anxiety, and encephalopathy (attributed to sedation for pain and anxiety).

iii) Deaths: There have been no deaths in this study.



iv) AESIs: Neither participant has reported GvHD. There has been no evidence of oligoclonality based on ISA.

*Reviewer comment: A total of 50 participants were treated with lovo-cel in the above three clinical trials (as of the data cut-off date) with a median duration of follow-up of 37.7 months (range=6.1-83.3 months). All fifty participants had successful neutrophil and platelet engraftment. Five AEs in five (5/50; 10%) participants were assessed by the sponsor as related or possibly-related to lovo-cel infusion: two events of anemia (subjects 206-(b) (6) [transfusion dependent anemia] and 206-(b) (6) and one event each of hot flush (subject 206-(b) (6), diastolic blood pressure decreased (subject 206-(b) (6), and AML (subject 206-(b) (6). The sponsor noted that individuals with SCD have an increased risk of hematologic malignancies and that pre-infusion conditioning with busulfan could also contribute to the risk of malignancy development. Please see the OTP clinical review memo for FDA's clinical assessment of adverse events. Please see Section 6.2 Safety-related Post-marketing Studies of this memo for additional details regarding participant follow-up in Study LTF-307.*

#### **5.2.4 Sponsor's 3-Month Safety Update Report**

The sponsor submitted a 3-month safety update report (STN 125788/0.2) that included data from three clinical trials and one LTFU study (LTF-307) for clinical trial participants. As of the data cut-off (February 13, 2023), 59 individuals were administered lovo-cel in the three clinical trials (HGB-205, HGB-206, and HGB-210) with a median duration of follow-up of 38.6 months (range=0.3-96.1 months; 49 participants have at least 18 months of follow-up). Among these 59 individuals, 47 were treated with product from the current manufacturing process and 45 are enrolled in study LTF-307. The sponsor also provided safety data from SAEs as of June 1, 2023.

Key findings included that there were two new cases of possible MDS identified, both of which occurred in the two participants in study HGB-206 with  $\alpha$ -thalassemia trait who experienced SAEs of anemia (see Section 5.2.2 above). Subject 206-(b) (6), a 19-year-old female who has ongoing transfusion dependent anemia, was initially diagnosed on Day 214 with MDS by the study investigator "based on persistent severe anemia and the finding of trisomy 8"; the investigator assessed this case as lovo-cel related. However, on Day 243 a repeat bone marrow biopsy showed no genetic or chromosomal abnormalities, and the study investigator revised the diagnosis of MDS to transfusion-dependent anemia. The sponsor commented that "on Day 613, an expert external hematopathologist concluded that the data demonstrated changes consistent with persistent hemoglobinopathy after transplant, with stress dyserythropoiesis."

Subject #206-(b) (6), 15-year-old male with  $\alpha$ -thalassemia trait who experienced SAEs of neutropenia and anemia on Day 373/374, had MDS reported on Day 925 (Month 30). The sponsor commented that external expert feedback indicated that the diagnosis of MDS has not been fully established and that the stable anemia and erythroid dysplasia "remain consistent with his underlying  $\alpha$ -thalassemia trait potentially exacerbated by treatment with lovo-cel." However, the sponsor noted that the hospital's tumor board "provided a consensus view that the subject satisfied the definition of MDS

due to persistent dysplasia in the erythroid lineage, persistent anemia, and new karyotypic clonal findings.” The participant is clinically well and has not required packed red blood cell transfusions since Day 28. This case of MDS was considered by the investigator as possibly related to lovo-cel and also “in part attributed to conditioning agent.” The sponsor agrees that the “AE of anemia may be partially related to lovo-cel.”

Also, there was a new SAE of bacteremia on Day 28 (subject 210-(b) (6) ) and two new non-serious infusion-related reactions (abdominal pain and nasal congestion; both in subject 210-(b) (6) ) that the sponsor considered related to lovo-cel. The sponsor noted there were no new deaths since the original BLA submission, no reports of primary or secondary graft failures, no acute or chronic GvHD, and no reports of insertional oncogenesis nor positive results for RCL.

*Reviewer comment: As of the sponsor’s 3-month safety update, there have been a total of two cases of AML following lovo-cel administration (subjects 206-(b) (6) and 206-(b) (6) ; both with fatal outcomes). The sponsor commented that neither case of AML represented insertional oncogenesis, although a “causative role for lovo-cel could not be excluded.” In addition, three cases of MDS were diagnosed during clinical studies (subjects 206-(b) (6) [also experienced fatal AML], 206-(b) (6) and 206-(b) (6) , although one of these cases (206-(b) (6) ) was subsequently revised by the study investigator to a diagnosis of transfusion-dependent anemia and one case (subject 206-(b) (6) ) was attributed by the study investigator to conditioning with busulfan. Please see the clinical review memo for FDA’s clinical assessment of cases of hematologic malignancy following lovo-cel administration.*

## **6 SPONSOR’S PHARMACOVIGILANCE PLAN (PVP)**

The sponsor submitted a PVP (BLA 125788/0; submitted on April 21, 2023) proposing routine PV activities, a long-term post-marketing registry study (REG-503) for patients who will receive the commercial product, and a LTFU study (LTF-307) for clinical trial participants who received the investigational product (Table 2). There are also ongoing clinical studies (Study HGB-206 and HGB-210). In addition, the sponsor proposes risk minimization activities, including routine risk communication (i.e., healthcare provider [HCP] education brochure and website, patient package insert, patient educational brochure, patient specific website, and outreach to patient advocacy groups) and the establishment of a limited number of treatment centers (including transplant center, apheresis collection center, and cell therapy lab) as Qualified Treatment Centers (QTCs). QTCs will be “qualified by bluebird bio to conduct specific activities related to administration of gene therapy products such as lovo-cel” and will ensure chain of identity of the patient’s cells, including transfer/receipt of the patient’s cells to/from the manufacturing site. Furthermore, QTCs will be educated on the USPI and patient labeling, including AE reporting.

*Reviewer comment: Should this product be approved, FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary at this time to ensure the benefits of lovo-cel outweigh its risks. Thus, the above described educational materials*

and designation of “qualified treatment centers” is not under an FDA required REMS; these are voluntary risk minimization strategies undertaken by the sponsor.

**Table 2. Sponsor’s Pharmacovigilance Plan (PVP)\***

Type of Concern	Safety Concern	Proposed Action
Important Identified	Hematologic malignancy	<ul style="list-style-type: none"> <li>• Routine and/or Additional PV Activity               <ul style="list-style-type: none"> <li>○ Routine PV</li> <li>○ Ongoing clinical studies, including LTFU Study LTF-307</li> <li>○ Registry Study (REG-503)</li> <li>○ Targeted questionnaire</li> </ul> </li> <li>• Risk Minimization Activity               <ul style="list-style-type: none"> <li>○ Routine risk communication (drug labeling and HCP and Patient Communication)</li> </ul> </li> </ul>
Important Potential	Insertional oncogenesis	<ul style="list-style-type: none"> <li>• Routine and/or Additional PV Activity               <ul style="list-style-type: none"> <li>○ Routine PV</li> <li>○ Ongoing clinical studies, including LTFU Study LTF-307</li> <li>○ Registry Study (REG-503)</li> </ul> </li> <li>• Risk Minimization Activity               <ul style="list-style-type: none"> <li>○ Routine risk communication (drug labeling and HCP and Patient Communication)</li> </ul> </li> </ul>
Important Potential	Lack or loss of response to gene therapy	<ul style="list-style-type: none"> <li>• Routine and/or Additional PV Activity               <ul style="list-style-type: none"> <li>○ Routine PV</li> <li>○ Ongoing clinical studies, including LTFU Study LTF-307</li> <li>○ Registry Study (REG-503)</li> </ul> </li> <li>• Risk Minimization Activity</li> <li>• Routine risk communication (drug labeling and HCP and Patient Communication)</li> </ul>
Important Potential	Neutrophil engraftment failure	<ul style="list-style-type: none"> <li>• Routine and/or Additional PV Activity               <ul style="list-style-type: none"> <li>○ Routine PV</li> <li>○ Ongoing study HGB-210</li> <li>○ Registry study (REG-503)</li> </ul> </li> <li>• Risk Minimization Activity               <ul style="list-style-type: none"> <li>○ Routine risk communication</li> </ul> </li> </ul>

		(drug labeling and HCP and Patient Communication)
Missing Information	Long-term safety and efficacy	<ul style="list-style-type: none"> <li>• Routine and/or Additional PV Activity <ul style="list-style-type: none"> <li>○ Routine PV</li> <li>○ Ongoing clinical studies, including LTFU Study LTF-307</li> <li>○ Registry study (REG-503)</li> </ul> </li> <li>• Risk Minimization Activity <ul style="list-style-type: none"> <li>○ Routine risk communication (drug labeling and HCP and Patient Communication)</li> </ul> </li> </ul>
Missing Information	Use in patients over 35 years of age	<ul style="list-style-type: none"> <li>• Routine and/or Additional PV Activity <ul style="list-style-type: none"> <li>○ Routine PV</li> <li>○ Ongoing clinical studies, including LTFU Study LTF-307</li> <li>○ Registry study (REG-503)</li> </ul> </li> <li>• Risk Minimization Activity <ul style="list-style-type: none"> <li>○ Routine risk communication (drug labeling and HCP and Patient Communication)</li> </ul> </li> </ul>
Missing Information	Pregnancy and lactation	<ul style="list-style-type: none"> <li>• Routine and/or Additional PV Activity <ul style="list-style-type: none"> <li>○ Routine PV</li> <li>○ Ongoing clinical studies, including LTFU Study LTF-307</li> <li>○ Registry study (REG-503)</li> </ul> </li> <li>• Risk Minimization Activity <ul style="list-style-type: none"> <li>○ Routine risk communication (drug labeling and HCP and Patient Communication)</li> </ul> </li> </ul>

\*Adapted from Pharmacovigilance Plan, Table 2, BLA 125788/0 (submitted on April 21, 2023), Module 1.16.1

## 6.1 Enhanced Pharmacovigilance

The sponsor also proposed routine PV activities beyond AE reporting and signal detection, including a targeted follow-up questionnaire for hematologic malignancy (e.g., MDS, AML, lymphoma), which will be used to obtain additional relevant information from HCPs, and expedited reporting for all individual case safety reports of hematologic malignancy in the post-marketing setting. The follow-up questionnaire will attempt to optimize data collection to better characterize malignancy events following

administration of lovo-cel. In addition, product labeling will direct HCPs to contact bluebird bio for instructions on collection of blood samples for further testing.

Reviewer comment: *The PVP includes a data collection tool for hematologic malignancy which includes patient demographics/weight/height, dosing/treatment information, relevant medical history, concomitant medications, and clinical/diagnostic testing/treatment related to hematologic malignancy. Note that the sponsor will submit expedited reports for all secondary malignancies, including hematologic malignancies (see reference to IR and response below).*

#### DPV IR #5 and #6

*IRs were sent acknowledging the sponsor's plans for expedited reporting of postmarketing cases of hematologic malignancy following administration of lovo-cel and requesting that they also perform expedited reporting for cases of any secondary malignancy in the postmarketing setting, including hematologic malignancy and cases of malignancy that occur post-lovo-cel infusion following allogeneic transplant.*

*The sponsor's IR responses (STN 125788/0.29 and 125788/0.33) acknowledged CBER's request for expedited reporting.*

## **6.2 Safety-related Post-marketing Studies**

### Post-marketing Registry Study (REG-503)

The sponsor proposes a prospective, observational post-marketing registry study (REG-503) in the U.S. with the primary objective to assess long-term safety, including the risk of newly diagnosed malignancies, after treatment with lovo-cel. The secondary objective is to evaluate the long-term effectiveness of treatment with lovo-cel in patients with SCD. The study will monitor for additional clinically important AEs not yet identified as part of the lovo-cel safety profile. Patients will be followed for 15 years post-infusion.

The primary safety endpoint is incidence of AEs of interest (AEIs) through 15 years post-lovo-cel infusion, including the following:

- Any newly diagnosed malignancies
- Any new or worsening hematologic disorders
- Any new or worsening neurologic disorders
- Immune-related AEs such as autoimmune disorders, GvHD, HIV, or opportunistic infections

Any SAE, AEI, or lovo-cel-related AE must be reported to the sponsor or designee within 24 hours of becoming aware of the event, including for newly diagnosed malignancies. In addition, any pregnancies that occur must be reported to the sponsor within 2-weeks of awareness; pregnancies will be followed for outcomes (including elective termination) and, for live births; infant status will be requested at 6 weeks of age and annually for two years. For any newly diagnosed malignancy or newly diagnosed

HIV-1, HIV-2, or human T-lymphotropic virus (HTLV), the sponsor will convene a safety review meeting to discuss appropriate follow-up and evaluations. If a newly diagnosed malignancy is detected, the sponsor (or designee) will facilitate clinical sample collection (if clinically feasible), including blood and bone marrow aspirate or biopsy specimens for analysis including ISA, to investigate if LVV integration could have contributed to the malignancy. If any patient is diagnosed with HIV-1, HIV-2, or HTLV, HCPs will be asked to provide the sponsor with blood samples to assess for potential presence of vector-derived RCL. In addition, the draft protocol includes protocol-driven laboratory assessments including a complete blood cell count with differential, peripheral blood ISA, vector copy number (VCN), and  $\beta^{A-T87Q}$ -globin analysis every 6 months post-lovo-cel infusion through Year 3 and then annually through Year 15.

The study plans to enroll a total of 250 patients with SCD who were treated in the post-market setting. The sponsor will work with the Center for International Blood and Marrow Transplant Research [CIBMTR] registry for clinical data collection. In addition, information will be requested from HCPs as needed to validate AEs and SAEs. Data analysis will be descriptive in nature; there are no formal study hypotheses and no sample size calculations. For the outcome measures of AEI, SAE, and lovo-cel related AEs, data analysis will include incidence rates or proportions with 2-sided 95% confidence intervals. Kaplan-Meier methods will be used to summarize overall survival, transplant-related mortality, and event-free survival.

The sponsor proposed the following milestones (STN 125788/0.7, IR response submitted on August 9, 2023):

- Final protocol submission: March 29, 2024
- Study completion: December 31, 2047
- Final study report: December 31, 2048

***Reviewer comment:** The sponsor proposes to begin data collection in 2024 and to submit interim study reports every 5 years. The sponsor submitted a draft study protocol and draft statistical analysis plan for the registry study. Lyfgenia utilizes a LVV and has potential for the serious risk of secondary malignancy due to replication-competent retrovirus or insertional mutagenesis; the sponsor assessed hematologic malignancy as an important identified risk in the PVP. As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the serious risk of secondary malignancy associated with Lyfgenia. The CBER Biologics Effectiveness and Safety (BEST) Program is not sufficient to characterize the serious risk of secondary malignancy since 15 years of follow-up, and collection of clinical samples and laboratory testing is needed; this is not feasible in available databases.*

*Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, the sponsor will be required to conduct a PMR safety study under FDAAA Title IX to identify the serious risk*

*of secondary malignancy after treatment with lovo-cel. The PMR will be conducted for 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020).*

*OBPV/DPV presented the PMR to the CBER SWG on October 12, 2023 and received SWG concurrence for requiring a PMR safety study to assess the serious risk of secondary malignancy following administration of lovo-cel. The sponsor was notified on November 2, 2023 that the registry study will be a PMR. The sponsor was asked to submit annual interim reports for REG-503 and provide their acknowledgement for the annual frequency of interim reports. In addition, the PMR notification letter advised the sponsor that we do not agree with their proposed study milestone dates and requested that they expedite the planned study completion timeline and submit revised study milestone dates. The sponsor's response (STN 125788/0.23) proposed the following revised study milestone dates:*

- Final protocol submission: March 29, 2024*
- Study completion: December 31, 2044*
- Final study report: December 31, 2045*

*In addition, the following IRs were sent regarding the sponsor's PV plans:*

*DPV IR #1:*

*We are reviewing the PVP for lovotibeglogene autotemcel submitted under BLA 125788/0 and have the following questions and comments:*

- 1. We note that the draft U.S. Package Insert (USPI) for lovotibeglogene autotemcel in "Section 8.7: Patients with Two  $\alpha$ -globin Gene Deletions" indicates that two patients who had comorbid sickle cell disease (SCD) and  $\alpha$ -thalassemia trait "had ongoing anemia after transplant, with erythroid dysplasia consistent with persistent hemoglobinopathy and stress erythropoiesis, hypothesized to be driven by  $\alpha$ -thalassemia trait, exacerbated by gene addition therapy with LYFGENIA." Please include an assessment of this sub-population (i.e., individuals with comorbid SCD and  $\alpha$ -thalassemia trait) in the proposed long-term follow-up registry study (REG-503).*
- 2. Neutrophil engraftment failure is listed in the PVP as an important potential risk. We note that platelet engraftment failure is not listed as a safety concern in the PVP. Please revise the important potential risk of "neutrophil engraftment failure" to "cytopenias due to engraftment failure," which would encompass the risk of both neutrophil and platelet engraftment failure.*
- 3. The PVP lists "insertional oncogenesis" as an important potential risk. We note that subject 206-(b) (6) was diagnosed with AML approximately 5.5 years post-lovo-cel infusion and integration site analysis of peripheral blood (collected on Day 2006) showed the VAMP4 integration site in 68.5% of cells. The Summary of Clinical Safety (page 63) indicates that the VAMP4 gene has "no*

*documented association with oncogenesis (including development of AML), cell replication, or cell cycle control” and was assessed as being a “non-causative passenger mutation in blast cells, and not a driver of insertional mutagenesis.” However, a current lack of documentation of association with oncogenesis for the VAMP4 integration site does not exclude a possible causative role in the development of AML in this individual. Please revise the PVP to include “insertional oncogenesis” as an important identified risk.*

- 4. The Integrated Summary of Safety (ISS) page 134 shows that individuals with SCD who were treated with Iovo-cel (n=50) had a median age=23.5 years (range=12-42 years). In addition, the draft USPI Section 8.4 states “The safety and efficacy of LYFGENIA in children less than 12 years of age have not been established. No data are available.” The PVP lists missing information “for use in patients over 35 years of age.” Please revise the PVP to also include “missing information” for “use in patients under 12 years of age.”*
- 5. Please provide milestone dates for the post-marketing registry study (REG-503) in MM/DD/YYYY format (using the last day of the month).*

*The sponsor’s IR response (STN 125788/0.7) is summarized below. For item #1, the sponsor agreed to perform a sub-group analysis in study REG-503 for subjects with two  $\alpha$ -globin gene deletions. The IR response for item #1 is acceptable.*

*For item #2, the sponsor proposed to maintain neutrophil engraftment failure as an important identified risk and add “prolonged thrombocytopenia” as a new important potential risk. The sponsor’s rationale was that there was no formal definition of platelet engraftment failure in the clinical study protocols or statistical plans and no definition of platelet engraftment failure was found in the literature. As of the 3-month safety update report, the median time to platelet engraftment was Day 39 (range=Day 19-136); three participants achieved platelet engraftment after Day 100. The sponsor’s revised PVP (submitted on August 9, 2023) includes “prolonged thrombocytopenia” as an important potential risk. Please see additional IR comments below under DPV IR #2.*

*For item #3, the sponsor proposed to maintain hematologic malignancy as an important identified risk and insertional oncogenesis as an important potential risk. The sponsor summarized the findings from their investigation of the two AML cases (subjects 206-(b) (6) and 206-(b) (6) from study HGB-206 and concluded that neither of the cases represented insertional oncogenesis. Note that FDA’s clinical assessment of these cases may differ from the sponsor’s assessment. Please see the FDA clinical review memo for FDA’s clinical interpretation of the data for these two cases of AML and potential causality related to insertional oncogenesis. The sponsor’s IR response for item #3 is acceptable for purposes of the PVP at this time.*

*For item #4, the sponsor agreed to add “use in patients under 12 years of age” as a missing information category; the revised PVP submitted on August 9, 2023 reflects this update. The IR response for item #4 is acceptable.*



*For item #5, the sponsor proposed the following milestone dates for the post-marketing registry study (REG-503): final protocol submission date of March 29, 2024; study completion date of December 31, 2047; and final report submission date of December 31, 2048.*

*DPV IR #2:*

*An IR was sent asking for further justification for the milestone dates for study REG-503 and to consider if earlier dates are possible. The sponsor's IR response (STN 125788/0.9) indicated that the proposed registry study milestones encompass a 15-year study duration and allow for time to enroll 250 individuals in the commercial setting. The sponsor commented that the milestone estimate is "complex" and is "influenced by multiple factors," including forecasted number of patients to be treated, number of patients consenting to participate in the study, and manufacturing capacity.*

*Reviewer comment:* *A follow-up IR was sent regarding the sponsor's proposed study milestone dates for REG-503:*

*BLA 125788 is under ongoing review and we have the following comment for the postmarketing requirement (PMR) study REG-503 milestone dates.*

*To reiterate, timely study completion is critical for postmarketing safety monitoring. And after considering study timelines for the indicated population, we ask you to revise the milestone dates for study REG-503 as follows:*

- No change to Final protocol submission date of March 29, 2024*
- Study completion date: revise to December 31, **2042***
- Final study report submission date: revise to December 31, **2043***

*Please provide your acknowledgement for the above timeline for Study REG-503 by 11/29/2023.*

*The sponsor's IR response (BLA 125788/0.29) proposed the following revised study milestones for REG-503, which are acceptable to the review team:*

- Final protocol submission: March 29, 2024*
- Study completion date: December 31, 2043*
- Final study report submission date: December 31, 2044*

*DPV IR #3:*

*In further collaboration with OTP clinical, the following IR was sent to the sponsor regarding the PVP and feedback on the registry study draft protocol:*

*Our review of your original BLA 125788/0 for lovotibeglogene autotemcel is ongoing. We have the following comments regarding your Pharmacovigilance Plan and proposed postmarketing long-term follow-up registry study (REG-503).*

### Pharmacovigilance Plan

1. We note that the Pharmacovigilance Plan submitted on August 9, 2023 includes “prolonged thrombocytopenia” as an important potential risk. A few clinical trial participants experienced delayed platelet engraftment. Please revise “prolonged thrombocytopenia” to “Delayed Platelet Engraftment” as an important identified risk.
2. Please add a version number and date to the Pharmacovigilance Plan for clarity in tracking and reference.
3. We acknowledge your plans for expedited reporting of postmarketing cases of hematologic malignancy.
4. In your periodic safety reports:
  - a. Please include a safety assessment (based on interval and cumulative postmarketing safety data) for the risk of all secondary malignancies, and specifically for hematologic malignancies. In your assessments, specify the data sources for reports of secondary malignancy, i.e., clinical trial data, or data from postmarketing safety study, or data from postmarketing spontaneous reports.
  - b. Please include a summary of any available interim reports for Study REG-503.

### Postmarketing Registry Study (REG-503)

1. Please include as a study objective, the characterization of hematologic malignancy that is secondary to lentiviral vector (LVV) insertional oncogenesis. The characterization is to include, but not be limited to, collecting the following data:
  - a. Risk factor identification (e.g., past medical history, family history, smoking, radiation/chemical/drug exposures).
  - b. Clinical progression of malignancy over time, from pre-diagnosis through treatment.
  - c. Characterization of response vs refractoriness to treatment including risk of relapse and death.
  - d. Characterization of molecular changes involved in the progression to malignancy and over what time period.
2. For all cases of malignancy and for HSCTs performed after lovo-cel administration for reasons other than malignancy, please collect the following information for inclusion in your interim and final study reports submitted to FDA:
  - a. Complete bone marrow biopsy/aspirate reports.
  - b. HSCT details, including cell source (e.g., cord, peripheral, or bone marrow), relationship (e.g., none, paternal, or sibling), HLA matching, and timing.
  - c. Conditioning including dose and timing (e.g., chemotherapy, immunosuppressives, total body irradiation).
  - d. Clinical course including serious adverse events and details/cause of any death.

- e. *In the event of relapse, provide timing, treatment, and outcome, and include details specified in items 2a through 2d above.*
3. *Please include additional protocol driven laboratory testing at baseline and post-lovo-cel infusion to allow for end organ damage assessment over time, including, but not limited to, kidney, cardiac, and pulmonary function testing.*
4. *Characterizing the risk of hematologic malignancy through this study necessitates the gathering of data through required assessments. Therefore, please modify the protocol to include the following routine assessments:*
  - a. *Upon enrollment into the study, the following tests are to be performed for all subjects to understand baseline risk for developing malignancy and to allow for comparison to future samples:*
    - i. *Bone marrow biopsy/aspirate*
    - ii. *Bone marrow Flow cytometry, FISH and karyotype*
    - iii. *Hematopathology review of peripheral blood smear*
    - iv. *Peripheral blood FISH and NGS*
    - v. *Complete count with differential*
    - vi. *Skin biopsy for assessment of germline mutations, if feasible*
  - b. *During the first year after lovo-cel:*
    - i. *Monthly complete blood count with differential*
    - ii. *Peripheral blood ISA and VCN at Months 6, 9, and 12*
    - iii. *Bone marrow biopsy/aspirate with ISA and hematopathology review of peripheral blood smear at Months 6 and 12 including FISH and NGS on PB*
  - c. *During Years 2 through 10 after lovo-cel - Every 4 months:*
    - i. *Complete blood count with differential and hematopathology review of peripheral blood smear*
    - ii. *Peripheral blood ISA and VCN*
    - iii. *Peripheral blood FISH and NGS*
  - d. *During Years 11 through 15 after lovo-cel – Every 6 months:*
    - i. *Complete blood count with differential and hematopathology review of peripheral blood smear*
    - ii. *Peripheral blood ISA and VCN*
    - iii. *Peripheral blood FISH and NGS*
5. *After the first year, for any CBC abnormality that is of Grade 2 or higher severity based on CTCAE classification, CBC should be repeated within one month.*
6. *After the first year, please incorporate bone marrow biopsy including ISA of bone marrow into the protocol at four-month intervals when any of the following is present:*
  - a. *Any two consecutive CTCAE grade II CBC values, adjusted for age*
  - b. *Any transfusion requirement*
  - c. *Abnormal results from the most recent bone marrow biopsy. Within your protocol, please describe what findings would constitute abnormal*

*results.*

*d. ISA relative frequency of  $\geq 5\%$  at two consecutive time points in a gene with known biological relevance to carcinogenesis*

*e. ISA relative frequency of  $\geq 10\%$  at two consecutive time points in a gene not known to have biological relevance to carcinogenesis*

*f. Please also propose a criterion based on percent change in overall VCN between two consecutive time points*

*7. Please perform gene expression studies to investigate changes in gene expression for instances of ISA relative frequency of  $\geq 5\%$  at two consecutive time points in a gene with known biological relevance to carcinogenesis.*

*8. Propose a strategy for identifying multiple integration sites within a clone. Please address what testing will be used, when it will be used, and how identification of multiple integration sites within a clone impacts the decision to perform a bone marrow biopsy.*

*9. Please collect detailed information about the lovo-cel product. In addition to your plans to collect lovo-cel lot number, drug product VCN, and drug product percent of vector-containing cells, please collect the number of cells administered and vector copies per transduced cell.*

*10. Please include a plan to collect details on hematopoietic recovery.*

*a. Please ensure all CBC data collected for the duration of a subject's enrollment in the study are recorded.*

*b. Please ensure a CBC is performed at every clinical visit in the first year.*

*c. Please record all transfusions and growth factor administration.*

*11. When performing RNA sequencing, please ensure the use of spike-in controls to allow proper normalization of gene expression.*

*12. For all bone marrow biopsies and peripheral blood smears, a single centralized hematopathology review is also needed.*

*13. All bone marrow biopsies should include core and aspirate to assess cellularity, fibrosis, and other relevant tests deemed by pathology, flow cytometry, conventional karyotyping, NGS, and ISA. FISH must be included if karyotype is abnormal.*

*14. Performance of cytogenetic/FISH and NGS studies should be centralized.*

*a. FISH should include a myeloid panel as well as probes for genes that have been implicated in LVV-mediated malignancy, such as MECOM. Please specify the FISH probes and NGS panels that will be utilized.*

*b. The NGS panel must be appropriate for age and include coverage for gene mutations expected in myeloid and lymphoid malignancies.*

15. Section 7.4.2.2 Blood Draws for Gene Therapy Specific Assessments. We note the draft protocol Figure 2 indicates that “Persistent oligoclonality triggers enhanced monitoring until patient no longer meets criteria for oligoclonality” and footnote “e” (page 27) states that “At a minimum, enhanced monitoring includes CBC with differential every 3 months and ISA & VCN every 6 months. Additional monitoring for malignancy may be instituted by the treating HCP.” Please further clearly define what additional monitoring for malignancy will be required and instituted when persistent oligoclonality is identified.

16. Section 7.5.3 In Case of Newly Diagnosed Malignancy: Please clearly define all additional studies that will be conducted for any malignancy occurrence, rather than including statements such as “may support collection of clinical samples,” “neoplastic tissue or autopsy tissue may also be requested,” and “VCN and ISA may be conducted.”

17. Section 7.9.4 Exploratory Endpoints: Please include incidence of VOE managed at home pre-and post-lovo-cel infusion as an exploratory efficacy endpoint. Please also include assessment of end organ damage over time post-lovo-cel infusion, including kidney, cardiac, and pulmonary function, as exploratory efficacy endpoints.

Please provide a response indicating your concurrence by November 3, 2023. As part of your response, please submit a revised PVP, in tracked change and clean versions, to incorporate FDA recommendations under section Pharmacovigilance Plan #1 – 4 and provide your acknowledgement and agreement with FDA recommendations for the postmarketing safety study REG-503 (final protocol to be submitted post-approval). Please submit responses via email to be followed by an official amendment to your BLA. Please include the above revisions in your final study protocol which should be submitted after BLA approval if the product is approved.

In the IR response (STN 125788/0.21) the sponsor agreed to the requested PVP updates and periodic safety report assessments and submitted a revised PVP (version 0.1, dated October 31, 2023). For study REG-503, the sponsor agreed to many of the clinical recommendations, but also raised concerns regarding testing burden for patients, undue procedure-associated risks (i.e., bone marrow biopsies), concerns that testing requirements might be a deterrent to patient enrollment and retention, and concerns that requests that do not align with current standard of practice. The sponsor’s IR response was shared with the OTP clinical team for their review and feedback.

#### DPV IR #4

A follow-up IR was sent to the sponsor regarding laboratory testing plans in study REG-503:

Please note that if additional protocol driven laboratory testing at baseline and post-lovo-cel infusion is not available for end organ damage assessment over time, and if baseline bone marrow biopsy/aspirate is not available, then:

- *long term AEs related to end organ damage, that develop after treatment and during the period of observation, will be attributed to lovo-cel*
- *all hematological malignancies that develop after the treatment and during the period of observation will be attributed to lovo-cel*

*Please include these assumptions in the final analysis of the study results.*

*The sponsor agreed with the above (STN 125788/0.29): “The Sponsor agrees that if protocol driven laboratory testing at baseline and post-lovo-cel infusion are not available for end organ damage assessment over time; all long-term AEs and SAEs related to end organ damage that occur post lovo-cel infusion will be considered attributed to lovo-cel. The Sponsor agrees that if baseline bone marrow biopsy/aspirate is not available; all hematologic malignancies post lovo-cel infusion will be attributed to lovo-cel. These assumptions will be included in the REG-503 Statistical Analysis Plan.” DPV will review the sponsor’s final study protocol for REG-503 including the Statistical Analysis Plan, upon submission post-BLA approval, should this BLA be approved.*

#### Long-Term Follow-up Study for Clinical Trials (LTF-307)

The sponsor is also conducting an ongoing LTFU study (LTF-307; IND 15905) with the objectives to evaluate long-term safety and efficacy of lovo-cel in individuals with SCD who are treated through clinical trials (i.e., HGB-205 and HGB-206). Participants will be followed for a total of 15 years (initial two years in the clinical trial and then 13-years of LTFU). Follow-up will be conducted every 6-months through Year 15 and will assess for safety concerns related to SAEs, drug-related product AEs, immune-related AEs, hematologic or neurologic disorders, hematologic malignancies, insertional oncogenesis, lack or loss of response to gene therapy, long-term safety and efficacy (including surveillance for evidence of RCL), and pregnancy and lactation. The primary study endpoints are as follows:

- Number of subjects with immune-related AEs (e.g., autoimmune disorders, GvHD, opportunistic infections, HIV)
- Number of subjects with new or worsening hematologic disorders
- Number of subjects with new or worsening neurologic disorders
- Number of subjects with malignancies

There are also secondary endpoints for VOEs (i.e., proportion with complete resolution of VOEs, annualized number of VOEs, change in annualized severe VOEs over time) and hematologic measures (i.e., measures of hemoglobin parameters and markers of hemolysis and iron stores). Participants will be tested for persistence of vector sequences, viral vector integration sites, and RCLs at pre-specified time points through Year 15. If all RCL tests are negative in the first year post-infusion, collection of yearly follow-up samples may be discontinued. However, if an AE develops that is suggestive of a retrovirus-associated disease, relevant clinical samples should be collected and RCL testing will be performed. If there is clonal predominance, persistent clonal predominance, or any clinical suspicion of a hematological malignancy (i.e.,

myelodysplasia, leukemia, or lymphoma), a work-up will be performed based on the standard of care which may include bone marrow analysis and cytogenetic and molecular analyses (e.g., fluorescence in situ hybridization, SNP microarray, karyotyping, or whole-genome sequencing). The protocol states that “All efforts should be made to confirm the source of malignancy.” Data analysis will be descriptive in nature and the safety analysis will focus on incidence of drug product related AEs, SAEs, and immune-related AEs, new or worsening hematologic or neurologic disorders, and malignancies during various time intervals.

The sponsor’s SCS indicates that 41 participants enrolled in study LTF-307. Two of these 41 participants developed AML and died from complications of AML (approximately 61.5 and 75.6 months post-infusion). One participant (subject 206-(b) (6)) was a 31-year old Black female who was diagnosed with AML approximately 5.5 years post-lovo-cel infusion and was treated with chemotherapy and then a haploidentical bone marrow transplant for refractory disease. ISA of peripheral blood (collected on Day 2006) showed a *VAMP4* integration site in 68.5% of cells although the “*VAMP4* expression was not altered in the blast cell-enriched cell population relative to the blast cell-depleted cell populations.” The SCS further states that “*VAMP4* is a gene with no documented association with oncogenesis (including development of AML), cell replication, or cell cycle control” and that next generation sequencing revealed variants of known AML driver genes (i.e., *RUNX1* frameshift mutation and *PTPN11* missense mutation). The sponsor assessed that the *VAMP4* integration site is a “non-causative passenger mutation in blast cells, and not a driver of insertional mutagenesis.” This individual experienced relapsed AML approximately 3-months post-bone marrow transplant, initiated salvage chemotherapy, and subsequently died of complications (i.e., respiratory failure) from relapsed AML approximately 6.5 years post-lovo-cel infusion. The study investigator assessed AML as related to busulfan and possibly related to lovo-cel. This individual also experienced recurrent leukemia that was considered possibly related to lovo-cel. The sponsor assessed AML in this individual as possibly related to lovo-cel. The sponsor concluded that AML in this individual was not due to insertional oncogenesis.

The second death related to AML occurred in a 46-year old Black male (subject 206-(b) (6)) who was diagnosed with MDS approximately 3-years post-infusion. No LVV integrations were detected by quantitative polymerase chain reaction. This individual developed AML approximately 5-months after the MDS diagnosis. The individual had a successful haploidentical transplant then subsequently experienced a relapse and died approximately 5 years post-lovo-cel infusion. The study investigator assessed the events of MDS and AML as possibly related to busulfan and not related to lovo-cel.

The sponsor commented in the SCS that the etiology of AML in the above two cases was determined to be multi-factorial and included the “underlying increased risk of hematologic malignancy in SCD, combined with the transplant procedure and associated proliferative stress, as well as continued hematologic stress due to the lack of clinical benefit from lovo-cel treatment.” The sponsor assessed that neither death case of AML represented insertional oncogenesis.

Thirty-nine participants continue to be followed with a median follow-up time of 42.9 months post-infusion (range=23.9-83.3 months). No participants experienced graft failure or acute/chronic GvHD and there were no new or worsening neurologic or autoimmune disorders considered related to lovo-cel by the sponsor. SAEs were commonly related to the underlying SCD. Two participants (subjects 206-(b) (6) and 206-(b) (6)) developed persistent oligoclonality which has not been associated with clinical malignancy. One additional participant (subject 206-(b) (6)), discussed above in this section) developed persistent oligoclonality associated with AML diagnosis approximately 5.5 years post-lovo-cel infusion; this participant is deceased. However, the sponsor reported that ISA determined the site was a “non-causative passenger mutation in the blast cells and not a driver of oncogenesis.”

*Reviewer comment: The duration and schedule of RCL testing is in accordance with FDA Guidance for Industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-Up (January 2020). The LTFU study will be conducted for up to 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020). OBPV defers to OTP for review of this LTFU study (LTF-307) for clinical trial participants. Please see the clinical review memo for FDA’s clinical assessment of cases of hematologic malignancy following lovo-cel administration.*

## **7 ANALYSIS OF SPONSOR’S PHARMACOVIGILANCE PLAN**

### **7.1 Important Identified Risks**

#### **7.1.1 Hematologic malignancy**

Hematologic malignancy may be associated with the underlying disease of SCD, transplant-related medications or procedures, hematologic proliferative stress, and could potentially result from expansion of gene-modified cells due to insertional oncogenesis. Two events of AML, both with fatal outcomes (subjects 206-(b) (6) and 206-(b) (6)), occurred in participants from study HGB-206 who were being followed in LTF-307 (see section 6.2); neither malignancy was determined by the sponsor to be due to insertional oncogenesis although a causative role for lovo-cel could not be excluded. In addition, three cases of MDS were diagnosed during clinical studies (subjects 206-(b) (6) [also experienced fatal AML], 206-(b) (6), and 206-(b) (6)), although one of these cases (206-(b) (6)) was subsequently revised by the study investigator to a diagnosis of transfusion-dependent anemia and one case (subject 206-(b) (6)) was attributed by the study investigator to conditioning with busulfan. Please see the clinical review memo for FDA’s clinical assessment of cases of hematologic malignancy following lovo-cel administration.

The important identified risk of hematologic malignancy, which can be fatal or life-threatening, will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities, including a



targeted questionnaire and expedited reporting of secondary malignancies, including hematologic malignancies. The sponsor will also submit a safety assessment for the risk of secondary malignancies, including hematologic malignancies, and provide a summary of available interim reports from study REG-503 in their periodic safety reports. In addition, the sponsor will monitor this risk in ongoing clinical studies and is conducting a LTFU study (LTF-307) for clinical trial participants. This safety concern will also be labeled in the USPI.

*Reviewer comment: Upon request from the OTP clinical team, the sponsor also submitted a Medication Guide. Please see the final label submitted by the sponsor for the final agreed upon language for the USPI. The proposed PVP is appropriate to monitor the identified risk of hematologic malignancy.*

### **7.1.2 Delayed Platelet Engraftment**

The sponsor indicated that platelet engraftment was defined in clinical studies as the “date of the first of three consecutive platelet count laboratory value of  $\geq 50 \times 10^9/L$  obtained on different days with no platelet transfusions administered for seven days immediately preceding and during the evaluation period.” As of the 3-month safety update report, the median time to platelet engraftment was Day 39 (range=Day 19-136); three participants achieved platelet engraftment after Day 100. Individuals with prolonged thrombocytopenia have a risk of bleeding and platelet recovery should be monitored closely. The important identified risk of delayed platelet engraftment will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor is also monitoring this risk in the ongoing clinical study HGB-210. This safety concern is labeled in the following sections of the USPI:

- Section 5.2, Warnings and Precautions
- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

*Reviewer comment: As requested by DPV, the sponsor’s revised PVP (version 0.1, dated October 31, 2023; STN 125788/0.21) includes the important identified risk of delayed platelet engraftment. The proposed PVP is appropriate to monitor the identified risk of delayed platelet engraftment.*

## **7.2 Important Potential Risks**

### **7.2.1 Insertional oncogenesis**

Insertional oncogenesis is a potential risk of treatment with lovo-cel as the product uses a LVV which integrates into the genome of transduced target cells. The sponsor reports that the LVV has design features to minimize the risk of insertional oncogenesis and the cellular promoter of the LVV is specific to erythroid lineage cells. The patient’s own HSCs are transduced *ex vivo*. Of note, one participant (subject 206-(b) (6)) in study HGB-206 was diagnosed with AML approximately 5.5 years post-lovo-cel infusion. ISA of peripheral blood showed a *VAMP4* integration site in 68.5% of cells although the

“*VAMP4* expression was not altered in the blast cell-enriched cell population relative to the blast cell-depleted cell populations.” The sponsor’s SCS states that “*VAMP4* is a gene with no documented association with oncogenesis (including development of AML), cell replication, or cell cycle control.” The sponsor assessed that the *VAMP4* integration site is a “non-causative passenger mutation in blast cells, and not a driver of insertional mutagenesis.” Please see the clinical review memo for FDA’s clinical assessment of this case.

The important potential risk of insertional oncogenesis will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor will also monitor this potential risk in ongoing clinical studies and is conducting a LTFU study (LTF-307) for clinical trial participants. This potential safety concern is labeled in the following sections of the USPI:

- Section 5.4, Warnings and Precautions: Insertional Oncogenesis
- Section 17, Patient Counseling Information

*Reviewer comment: The proposed PVP is appropriate to monitor the potential risk of insertional oncogenesis.*

## **7.2.2 Lack or loss of response to gene therapy**

Lovo-cel is a one-time gene therapy treatment and lack or loss of response to gene therapy is a potential risk. The sponsor indicates that available data has not identified a lack or loss of response to lovo-cel. The important potential risk of lack or loss of response to gene therapy will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor will also monitor this risk in ongoing clinical studies and is conducting a LTFU study (LTF-307) for clinical trial participants. The efficacy of Lyfgenia is discussed in Section 14 Clinical Studies of the USPI.

*Reviewer comment: The proposed PVP is appropriate to monitor the potential risk of lack or loss of response to gene therapy.*

## **7.2.3 Neutrophil engraftment failure**

Neutrophil engraftment failure is a potential risk following treatment with lovo-cel, although no participants experienced this event during clinical trials. If neutrophil engraftment failure were to occur, a patient would receive rescue therapy with a back-up collection of un-transduced autologous HSCs or receive an allo-HSC transplant. The important potential risk of neutrophil engraftment failure will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor is also monitoring this risk in the ongoing clinical study HGB-210. This safety concern is labeled in the following sections of the USPI:

- Section 5.3, Warnings and Precautions: Neutrophil Engraftment Failure
- Section 17, Patient Counseling Information

*Reviewer comment: The proposed PVP is appropriate to monitor and mitigate the potential risk of neutrophil engraftment failure.*

### **7.3 Important Missing Information**

#### **7.3.1 Long-term safety and efficacy**

The long-term safety and efficacy of lovo-cel is not known. The long-term safety and efficacy of lovo-cel will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor will also monitor this risk in ongoing clinical studies and is conducting a LTFU study (LTF-307) for clinical trial participants. The LTFU study is mentioned in the USPI Section 6.1 Clinical Trials Experience and Section 14 Clinical Studies.

*Reviewer comment: The proposed PVP is appropriate to address missing information for long-term safety and efficacy.*

#### **7.3.2 Use in patients over 35 years of age**

There is limited data on use of lovo-cel in individuals over 35 years of age. The safety of the product in individuals over 35 years of age will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor will also monitor this risk in ongoing clinical studies and is conducting a LTFU study (LTF-307) for clinical trial participants. The lack of information for use in older individuals is discussed in the following sections of the USPI:

- Section 8.5, Use in Specific Populations: Geriatric Use

*Reviewer comment: The proposed PVP is appropriate to address missing information in individuals over 35 years of age.*

#### **7.3.3 Use in patients below 12 years of age**

There is limited data on use of lovo-cel in individuals younger than 12 years of age. The safety of the product in individuals younger than 12 years of age will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor will also monitor this risk in ongoing clinical studies and is conducting a LTFU study (LTF-307) for clinical trial participants. The lack of information for use in younger individuals is discussed in the following sections of the USPI:

- Section 8.4, Use in Specific Populations: Pediatric Use

*Reviewer comment: The sponsor's revised PVP includes the missing information category for use in patients below 12 years of age (STN 125788/0.7, submitted on August 9, 2023). The proposed PVP is appropriate to address missing information in individuals under 12 years of age.*

### 7.3.4 Pregnancy and lactation

Lovo-cel has not been studied in pregnancy. Female study participants with child-bearing potential and male participants were required to use a reliable method of contraception from the time of screening through at least 6-months post-infusion. No pregnant participants received lovo-cel. Five participants in study HGB-206 had partners who became pregnant, four pregnancies occurred during long-term follow up and one occurred prior to cell collection; all partner pregnancies resulted in healthy full-term infants. The SCS indicates there is no information on the presence of lovo-cel in human milk, effects on breastfed infants, or effects on milk production and that no women who are pregnant or breastfeeding should receive lovo-cel.

The safety of the product in pregnancy and lactation will be monitored through a PMR LTFU registry study (REG-503) for recipients in the post-marketing setting, and through routine PV activities. The sponsor will also monitor this risk in ongoing clinical studies and is conducting a LTFU study (LTF-307) for clinical trial participants. The lack of information on use of Lyfgenia in pregnancy and lactation is discussed in the following sections of the USPI:

- Section 8.1, Use in Specific Populations: Pregnancy
- Section 8.2, Use in Specific Populations: Lactation
- Section 8.3, Use in Specific Populations: Females and Males of Reproductive Potential

*Reviewer comment: The proposed PVP is appropriate to address missing information in pregnancy and lactation.*

## 8 ADDITIONAL REVIEW TEAM PMR RECOMMENDATION

OTP made a determination that additional analysis was needed to assess a serious risk of patient exposure to any unknown extractables and leachables from the (b) (4) bag used to store and administer lovo-cel. Claims databases and available data sources in the CBER Biologics Effectiveness and Safety (BEST) System (also referred to as CBER Sentinel Program) are not sufficient to assess this serious risk. OTP presented an additional CMC study to the CBER SWG on October 12, 2023 and received SWG concurrence for a PMR under 505(o) of FDCA to evaluate leachables of the (b) (4) bag over the duration of the shelf-life of lovo-cel.

Note that OBPV defers to OTP for review of the above study.

## 9 DPV ASSESSMENT

Based on review of available data from Phase 1/2 and 3 clinical trials and an ongoing LTFU study of clinical trial participants, the safety concerns for lovo-cel warrant a FDAAA Title IX safety PMR registry study to assess the serious identified risk of secondary malignancies and long-term safety of lovo-cel. In addition, risks of treatment with lovo-cel will be addressed through routine risk

communication and risk minimization measures as recommended in the USPI. The sponsor will also conduct routine PV in accordance with 21 CFR 600.80 and enhanced PV for secondary malignancies, including use of a targeted follow-up questionnaire for hematologic malignancy and expedited reporting for all individual case safety reports of secondary malignancy, including hematologic malignancy, in the post-marketing setting. Furthermore, the sponsor will conduct a LTFU safety study (LTF-307) for individuals treated with lovo-cel in clinical trials. The above LTFU studies are in alignment with FDA Guidance Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020) available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products>.

## 10 DPV RECOMMENDATIONS

Should the product be approved for the treatment of patients 12 years of age or older with SCD and a history of VOs, the proposed PVP, version 0.1, dated October 31, 2023, is adequate to monitor the post-marketing safety for lovo-cel (Lyfgenia) which will include:

1. Routine PV, which includes AE reporting in accordance with 21 CFR 600.80
2. Enhanced PV for secondary malignancies, which includes expedited (15-day) reporting of secondary malignancies (regardless of seriousness or label status), including hematologic malignancies, following licensure. The sponsor will also provide a safety assessment of secondary malignancies in periodic safety reports, including a summary of any available interim reports for Study REG-503.
3. Safety-related postmarketing requirement (PMR) studies under 505 (o) of the FDCA: The review team and SWG have concurred with two FDAAA Title IX PMR studies.
  - a. A postmarketing, prospective, multi-center, 15-year LTFU observational safety study (REG-503), to assess the known serious risk of secondary malignancies following administration of lovo-cel. This study will enroll 250 SCD patients.
  - b. A study to evaluate leachables of the (b) (4) bag over the duration of the shelf-life of lovo-cel. OBPV defers to OTP for review of this study.

Should the BLA be approved, the PMR protocol REG-503 design and data analysis plan will be finalized with the sponsor post-licensure. Of note, an algorithm for monitoring for insertional oncogenesis, including a schedule for conducting ISA, and assumptions for interpretation of AEs when testing results may not be available, will be included in the REG-503 Statistical Analysis Plan and will be agreed upon. FDA has provided recommendations on the REG-503 study methods for the PMR, including the need for additional testing for safety outcome assessment and monitoring at pre-specified intervals. Testing will include bone marrow biopsy, peripheral blood sample analyses with blood

smear, ISA, vector copy number, and gene expression studies. FDA will review the final study protocol upon submission to ensure that FDA recommendations on study methods were appropriately incorporated.

In addition to the above PMRs, the sponsor is also conducting an ongoing LTFU study (LTF-307) to evaluate the long-term safety and efficacy of lovo-cel in individuals with SCD who received the investigational product in clinical trials. OBPV defers to OTP for review of Study LTF-307.

The available safety data do not substantiate the need for a REMS. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

## REFERENCES

1. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of Sickle Cell Disease. *Annu Rev Pathol.* 2019 Jan 24;14:263-292. doi: 10.1146/annurev-pathmechdis-012418-012838. Epub 2018 Oct 17. PMID: 30332562; PMCID: PMC7053558.
2. Vichinsky, EP. Overview of the clinical manifestations of sickle cell disease. Available at: [Overview of the clinical manifestations of sickle cell disease - UpToDate](#). Accessed on June 16, 2023.
3. Centers for Disease Control and Prevention. What is Sickle Cell Disease? Available at: [What is Sickle Cell Disease? | CDC](#). Accessed on June 16, 2023.
4. Centers for Disease Control and Prevention. Complications of Sickle Cell Disease. Available at: [Complications of Sickle Cell Disease | CDC](#). Accessed on June 16, 2023.
5. Centers for Disease Control and Prevention. Data and Statistics on Sickle Cell Disease. Available at: [Data & Statistics on Sickle Cell Disease | CDC](#). Accessed on June 16, 2023.

## APPENDIX

### Materials Reviewed

**Table A1: Materials reviewed in support of this assessment**

Date	Source	Document Type	Document(s) Reviewed
April 21, 2023	Sponsor	STN 125788/0	Module 1.16, Pharmacovigilance Plan
April 21, 2023	Sponsor	STN 125788/0	Module 1.14 Draft Labeling Text
April 21, 2023	Sponsor	STN 125788/0	Module 2.5 Clinical Overview
April 21, 2023	Sponsor	STN 125788/0	Module 2.7.4 Summary of Clinical Safety
April 21, 2023	Sponsor	STN 125788/0	Module 5.3.5.3 Integrated Summary of Safety
April 21, 2023	Sponsor	STN 125788/0	Module 5.3.5.4 Study Protocol REG-503 (version 1.0, dated January 23, 2023) and Statistical Analysis Plan (Version 1.0, dated January 23, 2023)
April 21, 2023	Sponsor	STN 125788/0	Module 5.3.5.2 Clinical Study Protocol LTF-307 (version 3.0, dated June 15, 2022)
July 19, 2023	Sponsor	STN 125788/0.2	Module 5.3 3-Month Safety Update Report
August 9, 2023	Sponsor	STN 125788/0.7	Module 1.16, Pharmacovigilance Plan
August 9, 2023	Sponsor	STN 125788/0.7	Module 1.11 Sponsor's IR response to DPV IR #1 regarding PV plans
August 22, 2023	Sponsor	STN 125788/0.9	Module 1.11 Sponsor's IR response to DPV IR #2 regarding milestone dates for post-marketing registry study REG-503
November 3, 2023	Sponsor	STN 125788/0.21	Module 1.11 Sponsor's IR response to DPV IR #3 regarding PVP and feedback on registry study draft protocol
November 3, 2023	Sponsor	STN 125788/0.21	Module 1.16 Pharmacovigilance Plan (version 0.1, dated October 31, 2023)
November 8, 2023	Sponsor	STN 125788/0.23	Module 1.11 Sponsor's IR response to PMR notification and request for expedited milestone dates for post-marketing registry study (REG-503)
November 29, 2023	Sponsor	STN 125788/0.29	Module 1.11 Sponsor's IR response regarding FDA requested study milestone dates for PMR post-marketing registry study (REG-503)
November 29, 2023	Sponsor	STN 125788/0.29	Module 1.11 Sponsor's IR response regarding request for expedited reporting for cases of any secondary malignancy in the post-market setting
December 1, 2023	Sponsor	STN 125788/0.33	Module 1.11 Sponsor's IR acknowledgement regarding request for follow-up testing and expedited reporting for

Date	Source	Document Type	Document(s) Reviewed
			all malignancies that occur following administration of lovo-cel, including in patients who may later receive allogeneic transplants