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Applicant	bluebird bio, Inc.
Established Name	lovotibeglogene autotemcel
(Proposed) Trade Name	LYFGENIA
Pharmacologic Class	Gene therapy (an autologous hematopoietic stem cell-based gene therapy)
Formulation(s), including Adjuvants, etc.	A single dose contains a minimum of 3.0×10^6 CD34+ cells/kg of body weight, in one or more infusion bags
Dosage Form(s) and Route(s) of Administration	Cell suspension for intravenous infusion
Dosing Regimen	The minimum recommended dose is 3.0×10^6 CD34+ cells/kg
Indication(s) and Intended Population(s)	Indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events

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LIST OF ABBREVIATION

AE	adverse event
allo-HSCT	allogeneic hematopoietic stem cell transplantation
BLA	Biologics License Application
CI	confidence interval
CRF	case report form
DMC	Data Monitoring Committee
DP	drug product
EAC	Event Adjudication Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GR	Globin Response
HSC	hematopoietic stem cell
ICF	informed consent form
iCSR	interim clinical study report
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	intent-to-treat
lovo-cel	lovotibeglogene autotemcel
pRBC	packed red blood cell(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCD	sickle cell disease
SD	standard deviation
SEP	successful engraftment population
sVOE	severe vaso-occlusive event
sVOE-CR	the complete resolution of sVOEs between 6 months and 18 months after drug product infusion
sVOE-CR24	complete resolution of sVOEs between 6 months and 24 months after drug product infusion
TDT	transfusion-dependent β -thalassemia
TEAE	treatment-emergent adverse event
TP	transplant population
TPVOE	transplant population for VOE
US	United States
VOE	vaso-occlusive event
VOE-CR	the complete resolution of VOEs between 6 months and 18 months after drug product infusion
VOE-CR24	the complete resolution of VOEs between 6 months and 24 months after drug product infusion

1. Executive Summary

The applicant (bluebird bio, Inc.) submitted an original Biologics License Application (BLA, STN 125788/0) for lovotibeglogene autotemcel (also referred to as lovo-cel), an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease (SCD) and a history of vaso-occlusive events.

Efficacy:

Study HGB-206, an open-label, single-dose, Phase 1/2 study, provided the principal evidence for clinical efficacy. The primary and key secondary efficacy analyses were conducted based on the interim data with cut-off date of February 13, 2023. The analyses were based on subjects in Group C who were treated with lovo-cel manufactured using the refined manufacturing process 2a.

- The primary efficacy endpoint was VOE-CR, defined as complete resolution (CR) of adjudicated vaso-occlusive events (VOEs) between 6 months and 18 months after lovo-cel infusion. The primary endpoint analysis showed that 28 of the 32 evaluable subjects in Group C transplant population for VOE (TPVOE) set achieved VOE-CR (87.5%; 2-sided 95% confidence interval [CI] of 71.0% to 96.5%).
- For the key secondary endpoint sVOE-CR (defined as the lack of any adjudicated severe VOEs between 6 months and 18 months after lovo-cel infusion), the analysis showed that 30 out of 32 evaluable subjects in Group C TPVOE set met the endpoint of sVOE-CR (93.8%; 2-sided 95% CI: 79.2%, 99.2%).
- The analysis of the key secondary endpoint Globin Response showed that 31 out of 36 evaluable subjects in Group C transplant population (TP) set (86.1%; 2-sided 95% CI: 70.5%, 95.3%) met the Globin Response endpoint.

Safety:

In Study HGB-206, the safety evaluation was focused on the subjects who initiated any study procedure for treatment under the current manufacturing Drug Process 2a (DP2a) (Group C), 100% (43/43) reported adverse events (AEs), 83.7% (36/43) of subjects reported treatment-emergent adverse events (TEAEs), and 9.3% (4/43) reported AEs related to drug product. Also, 76.7% (33/43) reported serious AEs (SAEs), 39.5% (17/43) of subjects reported treatment-emergent SAEs, and 4.7% (2/43) of subjects reported SAEs related to drug product. In the integrated safety analysis, the DP2a safety data pool included 59 subjects who initiated any study procedures for treatment under DP2a from Studies HGB-206, HGB-210, LTF-307 (BLA three-month safety update). The result showed that 100% (59/59) of subjects reported AEs, 79.7% (47/59) of subjects reported TEAEs, and 10.2% (6/59) of subjects reported Drug Product Related AEs. Additionally, 81.4% (48/59) of subjects reported SAEs, 44.1% (26/59) of subjects reported Treatment-Emergent SAEs, and 3.4% (2/59) reported Drug Product Related SAEs. In the DP2a pool, one subject died after lovo-cel administration; the death was not considered by the investigator to be related to lovo-cel.

In summary, the clinical efficacy data from Study HGB-206 provided adequate statistical evidence for clinical effectiveness of the product. No major safety concern was identified.

From the statistical perspective, the clinical efficacy and safety support approval of the product for the proposed indication.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Sickle cell disease. For more details, please refer to the clinical review.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Existing therapies include anti-sickling agents (e.g., hydroxyurea and voxelotor), packed red blood cell (pRBC) transfusions, downstream modifying agents (e.g., crizanlizumab and L-glutamine), and allogeneic hematopoietic stem cell transplantation (allo-HSCT).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

This product has not been licensed for use in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

This product was granted Orphan Drug Designation on February 27, 2014, Fast Track on May 08, 2014, Regenerative Medicine Advanced Therapy on October 26, 2017, and Rare Pediatric Disease Designation on May 14, 2020 from the Food and Drug Administration (FDA).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the clinical and bioresearch and monitoring (BIMO) reviews.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on Study HGB-206 which provides the principal efficacy evidence for the indication. Because the Phase 3 study HGB-210 is still ongoing and only 2 subjects initiated conditioning and were infused with drug product in the interim CSR, this study will be discussed in the context of integrated efficacy summary (ISE) in Section 7 of this memo.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- STN 125788/0.0 Module 2.5. Clinical Overview
- STN 125788/0.0 Module 2.7.3. Summary of Clinical Efficacy
- STN 125788/0.0 Module 2.7.4. Summary of Clinical Safety
- STN 125788/0.0 Module 5.3.5.2. Study HGB-206
- STN 125739/0.0 Module 5.3.5.2. Study HGB-210
- STN 125739/0.0 Module 5.3.5.2. Study HGB-205
- STN 125739/0.0 Module 5.3.5.2. Study LTF-307
- STN 125739/0.0 Module 5.3.5.3. Integrated Summary of Efficacy
- STN 125739/0.0 Module 5.3.5.3. Integrated Summary of Safety
- STN 125739/0.3 Module 1.11.3. Clinical Information Amendment – Response to clinical IR #01
- STN 125739/0.11 Module 1.11.3. Clinical Information Amendment – Response to clinical IR #05

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the studies conducted in the clinical development program.

Table 1. Summary of studies conducted in the clinical development program

Study Location	Objective(s) of the Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Planned Subjects <i>Treated, Completed^a</i>	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status
Phase 1/2 HGB-205 France	Safety, tolerability, success of engraftment, and quantification of gene transfer efficiency and expression Design: Nonrandomized, open-label, single-site, single-dose, uncontrolled	LentiGlobin BB305; Drug Product for SCD: $\geq 2.0 \times 10^6$ autologous transduced CD34+ hematopoietic stem cells/kg (bone marrow harvest) For β -thalassemia major: $\geq 3.0 \times 10^6$ autologous transduced CD34+ hematopoietic stem cells/kg (apheresis) Intravenous infusion	Planned: 7 (4 TDT and 3 SCD) to be treated (≥ 5 and ≤ 35 years of age) SCD: 3 treated, 3 completed study	SCD, Transfusion-dependent β -thalassemia (TDT)	Not applicable (single dose)	Completed
Phase 1/2 HGB-206 USA	Efficacy and safety Design: Nonrandomized, open-label, multi-site, single-dose, uncontrolled	bb1111 $\geq 2.0 \times 10^6$ autologous transduced CD34+ hematopoietic stem cells/kg (bone marrow harvest) Group C: $\geq 3.0 \times 10^6$ autologous transduced CD34+ hematopoietic stem cells/kg (apheresis) Intravenous infusion	Planned: approximately 50 SCD to be treated (≥ 12 and ≤ 50 years of age) 45 treated (7 in Group A, 2 in Group B, 36 in Group C), 38 completed study (7 in Group A, 2 in Group B, 29 in Group C)	SCD	Not applicable (single dose)	Ongoing; Interim Clinical Study Report
Phase 3 HGB-210 USA	Efficacy and safety Design: Nonrandomized, open-label, multi-site, single-dose, uncontrolled	bb1111 $\geq 3.0 \times 10^6$ autologous transduced CD34+ hematopoietic stem cells/kg Intravenous infusion	Planned: approximately 35 SCD to be treated (≥ 2 and ≤ 50 years of age) 2 treated, 0 completed study	SCD	Not applicable (single dose)	Ongoing; Interim CSR
Long- term follow- up LTF-307 France, USA	To extend the total time of observation post-drug product infusion to 15 years Design: Long-term follow-up study	No drug product administered in LTF-307	41 enrolled, 0 completed study	SCD	Not applicable	Ongoing; Interim CSR

Source: Adapted from Table 1 in Synopses of Individual Studies

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study HGB-206

Title: 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 (open-label, multi-site, single-dose, Phase 1/2 study in subjects ≥ 12 to ≤ 50 years of age with SCD)

6.1.1 Objectives

- Primary: To evaluate the efficacy of treatment with lovo-cel in subjects with severe SCD.
- Secondary: To evaluate the safety of treatment with lovo-cel in subjects with severe SCD.

6.1.2 Design Overview

This was an ongoing non-randomized, open label, multi-site, single dose, Phase 1/2 study in adults and adolescents with severe SCD. The study evaluated HSCT using lovo-cel, an autologous CD34+ cell-enriched population from patients with SCD that contains hematopoietic stem cells (HSCs) transduced with BB305 lentiviral vector (LVV) encoding a β^{A-T87Q} -globin gene. Treatment was divided into 4 stages: Stage 1 - Screening and eligibility assessment; Stage 2 - Stem cell harvest, drug product manufacture, and disposition; Stage 3 - Myeloablative conditioning and infusion of lovo-cel; Stage 4 - Follow-up for approximately 24 months after drug product infusion.

The applicant's interim clinical study report (iCSR) provided data on subjects who were divided into three groups based on stem cell harvest approach and drug product manufacturing process.

- Group A: both drug product and back-up cells were derived from bone marrow. Drug product was produced using manufacturing Process 1.
- Group B: bone marrow harvest as the cell source, a mixture of lots using Process 1 and Process 2.
- Group C: drug product was manufactured from plerixafor-mobilized cells collected by apheresis and using Process 2a.

Since Process 2a is considered as the refined manufacturing process for drug product, the efficacy analyses focus on Group C subjects who received the drug product manufactured with Process 2a.

An independent Event Adjudication Committee (EAC) was responsible for VOE assessment and determining whether an event met criteria for a VOE or sVOE for all reported events. The committee reviewed events that occurred prior to enrollment (retrospectively) as well as during the study. The committee was also responsible for the adjudication of any subject deaths after drug product infusion.

6.1.3 Population

Subjects must have been: ≥ 12 and ≤ 50 years of age at time of consent (or assent, as applicable), with SCD (diagnosis with either β^S/β^S , β^S/β^0 , or β^S/β^+ genotype); and for subjects < 18 years of age, a willing, matched human leukocyte antigen (HLA)-identical sibling hematopoietic cell donor is not available. Subjects must have experienced at least 4 severe vaso-occlusive events (sVOEs) in the 24 months prior to Informed Consent and failed to achieve adequate clinical benefit following hydroxyurea (HU).

6.1.4 Study Treatments or Agents Mandated by the Protocol

Lovo-cel is an autologous CD34+ cell-enriched population from patients with SCD that contains hematopoietic stem cells transduced with BB305 lentiviral vector (LVV) encoding the β^{A-T87Q} -globin gene, suspended in a cryopreservation solution.

6.1.6 Sites and Centers

The study was conducted at 11 clinical sites in the United States, as of August 11, 2022.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

- Primary efficacy endpoint: Complete resolution of vaso-occlusive events (VOE-CR), defined as complete resolution of VOEs between 6 months and 18 months after drug product infusion. In this study, a VOE was defined as any of the following events with or without hospitalization: an episode of pain with no medically determined cause other than a vaso-occlusion; acute chest syndrome (ACS); acute hepatic sequestration; acute splenic sequestration; and acute priapism. The success criterion was the lower limit of two-sided 95% CI for proportion of subjects who achieved VOE-CR being greater than 40%. Please see the reviewer's comment on the criterion in section 6.1.11.1.
- Key Secondary Efficacy Endpoints
 - sVOE-CR, defined as complete resolution of sVOEs, between 6 months and 18 months after drug product infusion. An sVOE was defined as a VOE requiring ≥ 24 -hour hospital or ER observation unit visit, or at least 2 visits to a day unit or ER over 72 hours with both visits requiring IV treatment, with the exception of priapism. The success criterion was the lower limit of two-sided 95% CI for proportion of subjects who achieved sVOE-CR being greater than 50%.
 - Globin Response, defined as meeting the following criteria for a continuous period of at least 6 months after drug product infusion: a) weighted average hemoglobin (Hb) A that contains β^{A-T87Q} -globin (HbA^{T87Q}) percentage of non-transfused total Hb $\geq 30\%$ AND b) weighted average non-transfused total Hb increase of ≥ 3 g/dL compared to baseline total Hb OR weighted average non-transfused total Hb ≥ 10 g/dL. The success criterion was the lower limit of two-sided 95% CI for proportion of subjects who achieved Globin Response being greater than 40%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Blinding and Randomization
This was a non-randomized, open-label study.
- Definitions of analysis populations

- Intent-to-Treat (ITT) Population: All subjects who initiated any study procedures, beginning with stem cell collection procedures (mobilization/apheresis or bone marrow harvest).
- Transplant Population (TP): All subjects who received drug product.
- Successful Engraftment Population (SEP): A subset of TP subjects who, following busulfan myeloablation and drug product infusion, successfully engraft with drug product, defined as 3 consecutive absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/\text{L}$ laboratory values obtained on different days after the initial post-infusion nadir by Day 43.
- Transplant Population for VOE (TPVOE): A subset of TP subjects with at least 4 Protocol VOEs in the 24 months prior to Informed Consent.

The primary efficacy endpoint (VOE-CR) and key secondary endpoint sVOE-CR were analyzed based on Group C subjects in TPVOE; the key secondary endpoint Globin Response was analyzed based on Group C subjects in TP. Safety endpoints are to be analyzed based on ITT or TP.

- Sample size planning

The sample sizes for Groups A and B were not determined by formal statistical methods. Approximately 41 subjects were planned to be enrolled in Group C, approximately 35 of whom must have met the sVOE criteria. For the primary endpoint, if 80% of Group C subjects who had at least 4 VOEs in the 24 months prior to Informed Consent (TPVOE Group C) met the primary efficacy endpoint VOE-CR, 35 subjects would provide more than 99% power to reject the null hypothesis of 40% at 1-sided α of 0.025.

- Statistical Analysis for Primary Efficacy Endpoint

For the primary efficacy endpoint, VOE-CR, responders of VOE-CR were subjects who did not have any adjudicated VOEs between 6 months and 18 months (i.e., 183 to 548 days) after drug product infusion. Non-responders of VOE-CR were subjects who met any of the following criteria: (1) Had ≥ 1 adjudicated VOE between 6 months and 18 months after drug product infusion. If a subject had an adjudicated VOE that occurred before 183 days but ended after 183 days after drug product infusion, the subject was considered as a non-responder. (2) Discontinued from the study on or before 18 months follow-up post-drug product infusion. The primary endpoint was to be analyzed in the TPVOE for Group C subjects. The percentage of subjects who achieved VOE-CR was to be presented with a 2-sided 95% CI using Clopper-Pearson method. The primary endpoint of VOE-CR was to be tested against the null hypothesis of 40%.

- Statistical Analysis for Key Secondary Efficacy Endpoints

- sVOE-CR

The key secondary endpoint sVOE-CR was analyzed in the TPVOE population for Group C subjects. This endpoint was to be tested against the null hypothesis of 50%. The number and percentage of subjects reaching the endpoint was to be presented along with the associated 2-sided 95% CI using the Clopper-Pearson method.

- Globin response

The key secondary endpoint of Globin Response was to be tested against the null hypothesis of 40%. The endpoint was to be analyzed in the TP for Group C subjects. The

number and percentage of subjects reaching the secondary endpoint was to be presented along with the associated 2-sided 95% CI using the Clopper-Pearson method.

- Multiplicity adjustment

Formal multiplicity adjustment was not planned.

- Missing data handling

A TPVOE subject was to be considered as a non-responder of VOE-CR or sVOE-CR if the subject discontinued from the study on or before 18 months follow-up post-drug product infusion. A TP subject was to be considered as a non-responder of Globin response if the subject did not achieve Globin Response before discontinuing from the study.

- Statistical Methods for Safety Analyses

The safety analyses were to be performed on subjects in all 3 groups in the ITT population or TP, as appropriate. Statistical methods for safety analysis were to be mainly descriptive.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Table 2 summarizes the demographic data for the ITT, TP, TP Group C, and TOVOE Group C, respectively. Of the 32 subjects in the TPVOE Group C, 24 subjects (75.0%) were ≥ 18 years to ≤ 50 years of age and 8 subjects (25.0%) were ≥ 12 to < 18 years of age. There were 20 male subjects (62.5%), 31 Black/African American subjects (96.9%), and 29 non-Hispanic subjects (90.6%) in the TPVOE Group C.

Table 2. Study HGB-206: Summary of Selected Demographics

Parameter	Statistic	ITT (N = 54)	TP (N = 45)	TP Group C (N = 36)	TPVOE Group C (N = 32)
Age at Informed Consent or Assent (years) ^a	n	54	45	36	32
	Median	25.0	25.0	24.0	25.0
	Min, Max	12, 43	12, 42	12, 38	12, 38
Age at Informed Consent or Assent (category) ^a					
≥ 18 years to ≤ 50 years	n (%)	45 (83.3)	37 (82.2)	28 (77.8)	24 (75.0)
≥ 12 years to < 18 years	n (%)	9 (16.7)	8 (17.8)	8 (22.2)	8 (25.0)
Sex					
Male	n (%)	34 (63.0)	30 (66.7)	22 (61.1)	20 (62.5)
Female	n (%)	20 (37.0)	15 (33.3)	14 (38.9)	12 (37.5)
Race					
Asian	n (%)	1 (1.9)	1 (2.2)	0	0
Black/African American	n (%)	48 (88.9)	43 (95.6)	35 (97.2)	31 (96.9)
White	n (%)	1 (1.9)	0	0	0
Multiracial	n (%)	2 (3.7)	0	0	0
Not Provided	n (%)	2 (3.7)	1 (2.2)	1 (2.8)	1 (3.1)
Ethnicity					
Hispanic	n (%)	2 (3.7)	1 (2.2)	1 (2.8)	1 (3.1)
Not Hispanic	n (%)	50 (92.6)	42 (93.3)	33 (91.7)	29 (90.6)
Not Provided	n (%)	2 (3.7)	2 (4.4)	2 (5.6)	2 (6.3)

Note: ^a Age of consent applicable for subjects ≥ 18 years of age; age of assent applicable for subjects <18 years of age.

Source: Original from Table 12 in Study HGB-206 iCSR

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The most frequently observed SCD genotype was homozygous for the β^S/β^S ; 98.1% [53/54] subjects, ITT), as expected for subjects with severe SCD. One subject (Subject (b) (6), Group C, ITT population) was heterozygous for the β^S mutation and a β^+ mutation (β^S/β^+); this subject discontinued before lovo-cel infusion. Please refer to the clinical review for detailed information. In the ITT population, the median of annualized number of protocol VOs in the 24 months prior to ICF was 3.50 (Min 0.0, Max 34.5); the median of annualized number of protocol sVOEs in the 24 months prior to ICF was 3.00 (Min 0.0, Max 16.0).

6.1.10.1.3 Subject Disposition

A total of 55 subjects were enrolled in the study and, of those 55 enrolled subjects, 54 subjects initiated stem cell collection and were therefore included in the ITT population (Table 3). Of the 54 subjects in the ITT population, 9 subjects discontinued prior to lovo-cel infusion, such that 45 subjects were treated with lovo-cel and included in the transplant population (TP).

Table 3. Study HGB-206: Summary of Disposition (ITT Population)

Parameter	Statistic	Group A (N = 9)	Group B (N = 2)	Group C (N = 43)	Overall (N = 54)
Subjects who initiated stem cell collection (ITT)	n (%)	9 (100.0)	2 (100.0)	43 (100.0)	54 (100.0)
Subjects who initiated conditioning (ITT)	n (%)	7 (77.8)	2 (100.0)	36 (83.7)	45 (83.3)
Subjects infused with lovo-cel (TP)	n (%)	7 (77.8)	2 (100.0)	36 (83.7)	45 (83.3)
Subjects with successful neutrophil engraftment (SEP)	n (%)	7 (77.8)	2 (100.0)	36 (83.7)	45 (83.3)
Transplant Population for VOE (TPVOE)	n (%)	6 (66.7)	2 (100.0)	32 (74.4)	40 (74.1)
Subjects who discontinued from study (ITT)	n (%)	2 (22.2)	0	8 (18.6)	10 (18.5)
Reasons for discontinuation:					
Withdrawal of consent	n (%)	1 (11.1)	0	4 (9.3)	5 (9.3)
Investigator decision	n (%)	1 (11.1)	0	2 (4.7)	3 (5.6)
Death	n (%)	0	0	1 (2.3)	1 (1.9)
Other	n (%)	0	0	1 (2.3)	1 (1.9)
Subjects who Completed the Study (ITT)	n (%)	7 (77.8)	2 (100.0)	29 (67.4)	38 (70.4)
Subjects who are Ongoing in Study (ITT)	n (%)	0	0	6 (14.0)	6 (11.1)

Source: Adapted from Table 8 in Study HGB-206 iCSR

6.1.11 Efficacy Analyses

All subjects who initiated any study procedures, beginning with stem cell collection, were included in the ITT population (N = 54) and were assessed for safety. All subjects who received lovo-cel were included in the TP (N = 45). Because different manufacturing conditions, efficacy analyses are stratified and presented by Group (A, B, or C) with the focus on the results obtained from subjects in Group C TP Group C (N = 36), who were treated with lovo-cel manufactured using the refined Process 2a. The VOE-related efficacy endpoints were assessed in a subset of TP subjects who had at least 4 Protocol VOEs within 24 months prior to Informed Consent (TPVOE; N = 32 for Group C). Having at least 4 Protocol VOEs at baseline was required per the Protocol inclusion criteria as of V8.0.

In Study HGB-206 iCSR (interim data cut August 11, 2022), the applicant indicated that subject 206-(b) (6) had not had at least 18 months of follow-up at the time of data cut-off for this iCSR, and thus the VOE-related efficacy analyses were conducted in a set of TPVOE evaluable subjects in Group C (N=31) and globin response was assessed in a set of TP evaluable subjects in Group C (N=35). However, the applicant reported that this subject had an sVOE of acute pain (non-cardiac chest pain) on Day 350 post-lovo-cel infusion in the 3-month safety update report (3MSUR, data cut-off date: February 13,

2023). Additionally, the applicant reported that this subject also met the key secondary endpoint of Globin Response as of February 13, 2023. According to the pre-specified non-responder definition in the SAP (see Section 6.1.9 of this memo), a subject should be considered to fail the VOE-CR endpoint if the subject experienced the event prior to the timepoint of interest regardless if the subject has completed the underlying period of follow-up. Therefore, subject 206-(b) (6) should be included in the analyses even though this subject did not have 18 months of follow-up at the February 2023 data lock

6.1.11.1 Analyses of Primary Endpoint

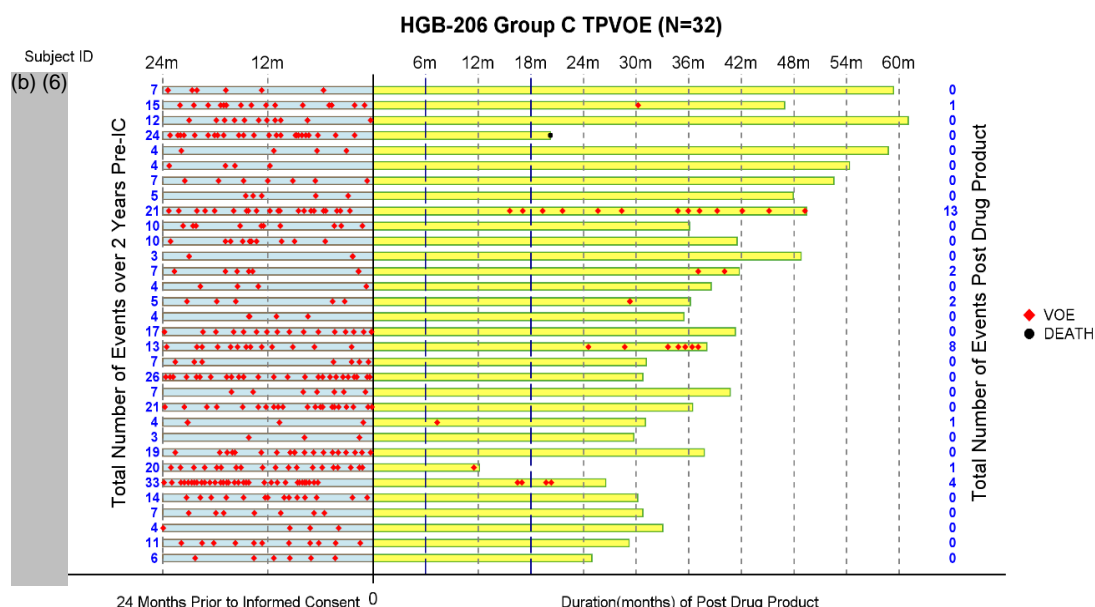
The primary efficacy endpoint for Study HGB-206 was VOE-CR, defined as complete resolution of adjudicated VOEs between 6 months and 18 months after lovo-cel infusion. The primary endpoint analysis was conducted based on Group C TPVOE evaluable set with data cut-off date of February 13, 2023 (N=32). Twenty-eight of the 32 evaluable subjects achieved VOE-CR (87.5%; 2-sided 95% CI of 71.0% to 96.5%) (Table 4; Figure 1). Additionally, the applicant reported that 27 out of 32 evaluable subjects in Group C TPVOE set met the endpoint of VOE-CR (84.4%; 2-sided 95% CI: 67.2%, 94.7%) between 6 months and 24 months after lovo-cel infusion.

Table 4. Study HGB-206: Adjudicated VOE-CR in the 6 to 18 Months Post-Lovo-cel Infusion (TPVOE-Evaluable Subjects in Group C)

Endpoint	Statistics	Adjudicated VOE-CR (N=32*)
Subjects who Achieved VOE-CR	n (%)	28 (87.5)
	2-sided 95% CI	71.0%, 96.5%

Source: Table 1 in the applicant's response to IR#5, dated August 29, 2023 (Amendment 125788/0.11).

Figure 1. Study HGB-206: Adjudicated VOEs over time (TPVOE - Evaluable Subjects, Group C)



Source: Generated by the reviewer based on the data with cut-off date of February 13, 2023 (Amendment 125788/0.3)

Reviewer Comment:

- The applicant proposed the success criterion for the primary efficacy analysis - the lower limit of two-sided 95% CI for the proportion of subjects who achieved VOE-CR being greater than 40% during the IND stage. CBER did not agree with the proposed criterion. Nevertheless, the primary efficacy endpoint result showed that the proportion of subjects who achieved VOE-CR was 84.4% with 2-sided 95% CI (67.2%, 94.7%), which is considered to have demonstrated clinical efficacy.
- The primary efficacy endpoint analysis was conducted on the TPVOE evaluable population which was a subset of TP subjects who had at least 4 Protocol VOEs within 24 months prior to Informed Consent. Since the primary efficacy endpoint analysis was based on adjudicated VOEs, a sensitivity analysis was conducted on the TP subjects who had at least 4 adjudicated VOEs within 24 months prior to Informed Consent (N=30). In this analysis, 26 out of 30 subjects met the endpoint of VOE-CR (86.7%; 2-sided 95% CI: 69.3%, 96.2%).
- The primary efficacy endpoint analysis evaluated adjudicated VOEs in the TPVOE evaluable population between 6 and 18 months after lovo-cel infusion. Between 18 and 24 months, subject 206-(b) (6) died due to an event of Sudden death and was considered as a non-responder. After 24 months after lovo-cel infusion, 4 additional subjects had adjudicated VOEs (Figure 1).

6.1.11.2 Analyses of Key Secondary Endpoints

- sVOE-CR

sVOE-CR, defined as the lack of any adjudicated sVOEs between 6 months and 18 months after lovo-cel infusion. As of the data cut-off February 13, 2023, 32 subjects in TPVOE Group C were evaluable for this endpoint. The analysis showed that 30 out of 32 evaluable subjects in Group C TPVOE set met the endpoint of sVOE-CR (93.8%; 2-sided 95% CI: 79.2%, 99.2%) (Table 5). Additionally, the applicant reported that 29 out of 32 evaluable subjects in Group C TPVOE set met the endpoint of sVOE-CR (90.6%; 2-sided 95% CI: 75.0%, 98.0%) between 6 months and 24 months after lovo-cel infusion.

Table 5. Study HGB-206: sVOE-CR in the 6 to 18 Months Post-Lovo-cel Infusion (TPVOE – Evaluable Subjects in Group C)

Endpoint	Statistics	Adjudicated sVOE-CR (N=32*)
Subjects who Achieved sVOE-CR	n (%)	30 (93.8)
	2-sided 95% CI	79.2%, 99.2%

Source: Table 1 in the applicant's response to IR#5, dated August 29, 2023 (Amendment 125788/0.11).

- Globin response

The Globin response endpoint analysis was conducted based on Group C TP evaluable set with data cut-off date of February 13, 2023 (N=36). As shown in Table 6, 31 out of 36 evaluable subjects (86.1%, 95% CI: 70.5%, 95.3%) met the Globin Response endpoint.

Table 6. Study HGB-206: Globin Response (TP – Evaluable Subjects in Group C)

Endpoint	Statistic	HGB-206 Group C (N = 36)
Subjects Who Achieved Globin Response	n (%)	31 (86.1)
	2-sided 95% CI	70.5%, 95.3%

Source: Table 5 in the applicant's response to IR#1, dated July 12, 2023 (Amendment 125788/0.3).

6.1.11.3 Subpopulation Analyses

Because 35 of 36 TP Group C subjects were Black/African American, subgroup analysis for the primary and key secondary endpoints was not conducted by race but only conducted by sex and age (Table 7). Percentages of subjects who met VOE-CR, sVOE-CR, and Globin response were higher in male subjects than female subjects. These percentages were generally similar between age groups.

Table 7. Study HGB-206: Subgroup analysis of the primary and key secondary efficacy endpoints by sex and age

	Subgroup	VOE-CR TPVOE Evaluable Subjects in Group C (N=32)	sVOE-CR TPVOE Evaluable Subjects in Group C (N=32)	Globin Response TP Evaluable Subjects in Group C (N=36)
Sex	Male	20/20 (100%)	20/20 (100%)	20/22 (90.9%)
	Female	8/12 (66.7%)	10/12 (83.3%)	11/14 (78.6%)
Age	≥ 18 Years of Age	20/24 (83.3%)	22/24 (91.7%)	24/28 (85.7%)
	≥ 12 to < 18 Years of Age	8/8 (100%)	8/8 (100%)	7/8 (87.5%)

Source: Reviewer's analysis based on the data with cut-off date February 13, 2023.

Reviewer Comment: The subgroup analysis showed that the percentages of subjects who met VOE-CR, sVOE-CR, and Globin response were higher in male subjects than female subjects. The subgroup analysis was descriptive and cannot be used to draw a firm statistical conclusion. I defer to the clinical reviewer on clinical implications of the observed differences.

6.1.11.4 Dropouts and/or Discontinuations

In Group C, 7 subjects discontinued before conditioning was initiated. One subject (206-(b) (6)) discontinued after drug product infusion due to an SAE of sudden death that was considered by the investigator to be unlikely related to the drug product.

6.1.12 Safety Analyses

A summary of AEs and SAEs for the ITT population (from signing the informed consent through last follow-up) is presented in Table 8 (data cut-off date August 11, 2022). In Group C, 100% of subjects had at least 1 AE; 9.3% of subjects had at least 1 AE related to drug product.

Table 8. Study HGB-206: Summary of Adverse Events (ITT Population)

	Group A (N = 9)	Group B (N = 2)	Group C (N = 43)	Overall (N = 54)
Adverse Events	n (%), Events	n (%), Events	n (%), Events	n (%), Events
Subjects with at Least 1 AE	9 (100.0), 548	2 (100.0), 133	43 (100.0), 2195	54 (100.0), 2876
Subjects with at Least 1 TEAE	7 (77.8), 282	2 (100.0), 61	36 (83.7), 1405	45 (83.3), 1748
Subjects with at Least 1 AE Attributed to Cell Procurement	9 (100.0), 43	2 (100.0), 9	23 (53.5), 89	34 (63.0), 141
Subjects with at Least 1 AE Attributed to Conditioning	7 (77.8), 101	2 (100.0), 33	36 (83.7), 777	45 (83.3), 911
Subjects with at Least 1 AE Related to Drug Product	0	1 (50.0), 1	4 (9.3), 13	5 (9.3), 14
Subjects with at Least 1 AE Related to SCD	9 (100.0), 210	2 (100.0), 55	41 (95.3), 662	52 (96.3), 927
Serious Adverse Events				
Subjects with at Least 1 SAE	9 (100.0), 74	2 (100.0), 21	33 (76.7), 182	44 (81.5), 277
Subjects with at Least 1 TESAE	6 (66.7), 36	2 (100.0), 8	17 (39.5), 59	25 (46.3), 103
Subjects with at Least 1 SAE Attributed to Cell Procurement	2 (22.2), 3	1 (50.0), 3	6 (14.0), 6	9 (16.7), 12
Subjects with at Least 1 SAE Attributed to Conditioning	2 (22.2), 3	1 (50.0), 1	6 (14.0), 8	9 (16.7), 12
Subjects with at Least 1 SAE Related to Drug Product	0	0	2 (4.7), 9	2 (3.7), 9
Subjects with at Least 1 SAE Related to SCD	7 (77.8), 62	2 (100.0), 14	25 (58.1), 123	34 (63.0), 199

Source: adapted from Table 68 in Study HGB-206 iCSR

6.1.12.1 Methods

Descriptive methods were used for safety analyses.

6.1.12.3 Deaths

As of the data cut-off date August 11, 2022, one subject (1/54, 1.9%) in the ITT population (Group C) had a fatal TEAE which was not considered by the applicant to be related to drug product.

6.1.12.4 Nonfatal Serious Adverse Events

In Group C, 76.7% of subjects had at least 1 SAE; 4.7% of subjects had at least 1 SAE related to drug product.

6.1.12.7 Dropouts and/or Discontinuations

In Group C, one subject discontinued due to sudden death. Please see Section 6.1.12.3.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

7.1.1 Methods of Integration

The applicant pooled the efficacy data by drug product manufacturing process and overall SCD. The drug process pools include subjects who received Drug Process 2a (DP2a), and subjects who received any previous Drug Processes (0, 1, and 2, abbreviated as DP0/1/2). For the integrated efficacy analysis, this review focuses on the DP2a pool which includes Study HGB-206 Group C and Study HGB-210.

Study HGB-210 is a non-randomized, open-label, multi-site, single-dose, Phase 3 study in adults and pediatric subjects ≥ 2 and ≤ 50 years of age with SCD. Approximately 35 subjects were planned to be treated. The primary endpoint of this study is the proportion of subjects achieving VOE-CR, defined as complete resolution of VOEs between 6 months and 18 months after drug product infusion. At the interim data cut-off for this interim analysis (August 1, 2022), 2 subjects had been treated with lovo-cel (and enrollment is ongoing).

7.1.2 Demographics and Baseline Characteristics

Table 9 summarizes demographic information of Study HGB-206 Group C, HGB-210, and DP2a pool.

Table 9. ISE: Selected Demographic Parameters for the DP2a Pool

Parameter	Statistic	HGB-206 Group C N = 36	HGB-210 N = 2	Pooled N = 38
Age at Informed Consent or assent (years)	n	36	2	38
	Median	24.0	16.0	23.5
	Min, Max	12, 38	15, 17	12, 38
Age at Informed Consent or assent ≥ 18 years	n (%)	28 (77.8)	0	28 (73.7)
≥ 12 to < 18 years	n (%)	8 (22.2)	2 (100.0)	10 (26.3)
Sex				
Male	n (%)	22 (61.1)	1 (50.0)	23 (60.5)
Female	n (%)	14 (38.9)	1 (50.0)	15 (39.5)
Race				
Asian	n (%)	0	0	0
Black/African American	n (%)	35 (97.2)	2 (100.0)	37 (97.4)
White	n (%)	0	0	0
Not Reported	n (%)	1 (2.8)	0	1 (2.6)
Ethnicity				
Hispanic	n (%)	1 (2.8)	0	1 (2.6)
Not Hispanic	n (%)	33 (91.7)	2 (100.0)	35 (92.1)
Not Reported	n (%)	2 (5.6)	0	2 (5.3)

Source: Adapted from Table 6 in Summary of Clinical Efficacy

7.1.4 Analysis of Primary Endpoint

As compared with Study HGB-206 Group C, Study HGB-210 added two subjects into the DP2a pooled analysis. In the DP2a analysis, 30 of the 34 evaluable subjects achieved VOE-CR (88.2%; 2-sided 95% CI of 72.5% to 96.7%) (Table 10). The result showed a similar trend as Study HGB-206 Group C; the lower limit of 95% CI met the success threshold of 40%.

Table 10. ISE: VOE-CR in the 6 to 18 Months Post-Infusion (TPVOE – Evaluable Subjects in DP2a Pool)

Parameter	Statistic	HGB-206 Group C (N = 32*)	HGB-210 (N = 2)	DP2a (N = 34*)
Subjects Who Achieved Adjudicated VOE-CR	n (%)	28 (87.5)	2 (100.0)	30 (88.2)
	2-sided 95% CI	71.0, 96.5	15.8, 100.0	72.5, 96.7
Subjects Who Achieved Adjudicated sVOE-CR	n (%)	30 (93.8)	2 (100.0)	32 (94.1)
	2-sided 95% CI	79.2, 99.2	15.8, 100.0	80.3, 99.3

Note: * Subject 206-(b) (6) was included in the Group C TPVOE evaluable set for VOE-related analyses (data cut-off date: Feb. 13, 2023)

Source: Adapted from Table 9 and Table 13 in Summary of Clinical Efficacy. Results were updated by the reviewer for Study HGB-206 Group C and DP2a with the data with cut-off date February 13, 2023.

7.1.5 Analysis of Secondary Endpoints

- sVOE-CR

In the DP2a analysis, 32 of the 34 evaluable subjects achieved sVOE-CR (94.1%; 2-sided 95% CI of 80.3% to 99.3%) (Table 10).

- Globin Response

In the DP2a analysis, 33 of the 38 evaluable subjects achieved Globin response (86.8%; 2-sided 95% CI of 71.9% to 95.6%) (Table 11).

Table 11. ISE: Globin Response (TP – Evaluable Subjects in DP2a Pool)

Parameter	Statistic	HGB-206 Group C (N = 36)	HGB-210 (N = 2)	DP2a Overall (N = 38)
Subjects Who Achieved Globin Response	n (%)	31 (86.1)	2 (100.0)	33 (86.8)
	2-sided 95% CI	70.5, 95.3	15.8, 100.0	71.9, 95.6

Source: Table 5 in the applicant's response to IR#1, dated July 12, 2023 (Amendment 125788/0.3).

7.1.11 Efficacy Conclusions

In the integrated efficacy analyses based on the DP2a Pool, the primary and key secondary efficacy endpoint results showed similar trends as those in Study HGB-206 and met the respective success thresholds.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The applicant performed integrated safety analysis using 3 pools for subjects with SCD: an SCD Pool that includes all subjects, and 2 pools based on drug product manufacturing process, DP0/1/2 and DP2a, as shown in Table 12.

Table 12. ISS: Pooling of SCD Safety Data by Parent Study

Study	Drug Product Manufacturing/ Cell Source	DP0/1/2	DP2a	SCD
HGB-205 (SCD)	Process 0/ bone marrow harvest	X		X
HGB-206 (Group A)	Process 1/ bone marrow harvest	X		X
HGB-206 (Group B1)	Process 1 & Process 2/ bone marrow harvest	X		X
HGB-206 (Group B2)	Process 2/ bone marrow harvest	X		X
HGB-206 (Group C)	Process 2a/ mobilization & apheresis		X	X
HGB-210	Process 2a/ mobilization & apheresis		X	X

Source: Table 2 in the Integrated Summary of Safety

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The DP2a pool includes Studies HGB-206 (Group C), its long-term follow-up study LTF-307 and HGB-210.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The manufacturing process for lovo-cel was refined over time based upon bluebird bio process development studies. The subjects who were exposed to the early processes (Processes 0, 1, and 2) were pooled into the DP0/1/2 Pool and those using Process 2a and mobilized cells were pooled into the DP2a Pool. The SCD Pool is a combination of DP0/1/2 and DP2a pools. The application used the SCD pool to evaluate the potential risks associated with gene therapy product in the patient population, regardless of drug product manufacturing process or method of stem cell procurement.

This review focuses on DP2a pool. As of the data cut-off date for the three-month safety update (13 February 2023), 59 subjects started mobilization or bone marrow harvest, of which 47 subjects were treated with the current manufacturing process DP2a, 36 subjects completed the parent study, and 33 subjects were enrolled into the long-term follow-up

study LTF-307. For the subjects who were treated with DP2a (N=47), the median length of follow-up post infusion was 35.45 months (Min 0.3, Max 61.0).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

N.A.

8.4 Safety Results

8.4.1 Deaths

Three subjects died after lovo-cel administration (One subject in the DP2a pool and two subjects in the DP0/1/2 pool). None of the deaths were considered by the investigator to be related to lovo-cel.

8.4.2 Nonfatal Serious Adverse Events

Overall, 62 out of 73 subjects (84.9%) in the SCD pool reported SAEs. In the DP0/1/2 pool, 14 out of 14 subjects (100%) reported SAEs; In the DP2a pool, 48 out of 59 subjects (81.4%) reported SAEs (Table 13). Additionally, 1 out of 14 subjects (7.1%) reported drug-related SAE in the DP0/1/2 pool, and 2 out of 59 subjects (3.4%) reported drug-related SAEs in the DP2a pool.

Table 13. ISS: Overview of Adverse Events: SCD, DP0/1/2 and DP2a Pools (ITT Population)

Parameter Number (%) of Subjects with at Least 1 Event, Number of Events	DP0/1/2 (N=14) n (%), E	DP2a (N=59) n (%), E	SCD (N=73) n (%), E
Adverse Event	14 (100.0), 921	59 (100.0), 2804	73 (100.0), 3725
Treatment-Emergent (TE) Adverse Event	12 (85.7), 530	47 (79.7), 1632	59 (80.8), 2162
Grade ≥3 Adverse Event	14 (100.0), 308	57 (96.6), 578	71 (97.3), 886
Grade ≥3 TE Adverse Event	12 (85.7), 220	44 (74.6), 350	56 (76.7), 570
Serious Adverse Event	14 (100.0), 221	48 (81.4), 277	62 (84.9), 498
TE Serious Adverse Event	12 (85.7), 165	26 (44.1), 97	38 (52.1), 262
Drug Product Related Adverse Event	2 (14.3), 3	6 (10.2), 17	8 (11.0), 20
Drug Product Related Serious Adverse Event	1 (7.1), 2	2 (3.4), 10	3 (4.1), 12
Adverse Event Leading to Study Discontinuation	2 (14.3), 2	1 (1.7), 1	3 (4.1), 3
Adverse Event Resulting in Death	2 (14.3), 2	1 (1.7), 1	3 (4.1), 3

Source: Table 1.2.1.2 in the three-month safety update ISS-Tables-Listings-Figures

8.4.3 Study Dropouts/Discontinuations

In the DP0/1/2 pool, 2 out of 14 subjects (14.3%) discontinued from study due to AEs. In the DP2a pool, 1 out of 59 subjects (1.7%) discontinued from study due to AEs (Table 13).

8.4.4 Common Adverse Events

Overall, 73 out of 73 subjects (100%) reported AEs in the SCD pool. In the DP0/1/2 pool, 14 out of 14 subjects (100%) reported AEs; in the DP2a pool, 59 out of 59 subjects (100%) reported AEs (Table 13).

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

- Efficacy:

Study HGB-206 provided the principal evidence for clinical efficacy. In Study HGB-206 iCSR (interim data cut August 11, 2022), the applicant indicated that subject 206-^{(b) (6)} had not had at least 18 months of follow-up at the data cut-off time for the iCSR, and thus the VOE-related efficacy analyses were conducted in a set of TPVOE evaluable subjects in Group C (N=31) and globin response was assessed in a set of TP evaluable subjects in Group C (N=35), excluding this subject. However, the applicant reported that this subject had an sVOE on Day 350 post-lovo-cel infusion in the 3-month safety update report (data cut-off date: February 13, 2023). Additionally, the applicant reported that this subject also met the key secondary endpoint of Globin Response as of February 13, 2023. Therefore, this subject was included in the revised primary and key secondary endpoint analyses even though this subject did not have 18 months of follow-up at February 2023 data lock.

- The primary efficacy endpoint was VOE-CR, defined as complete resolution of adjudicated VOEs between 6 months and 18 months after lovo-cel infusion. The primary endpoint analysis was conducted based on Group C TPVOE evaluable set (N=32). Twenty-eight of the 32 evaluable subjects achieved VOE-CR (87.5%; 2-sided 95% CI of 71.0% to 96.5%).
 - For the key secondary endpoint sVOE-CR, 32 subjects in TPVOE Group C were evaluable for this endpoint. The analysis showed that 30 out of 32 evaluable subjects in Group C TPVOE set met the endpoint of sVOE-CR (93.8%, 95% CI 79.2%, 99.2%).
 - The analysis of the secondary endpoint Globin Response showed that 31 out of 36 evaluable subjects (86.1%, 95% CI: 70.5%, 95.3%) met the Globin Response endpoint.
- Safety:

In Study HGB-206, the safety evaluation was focused on the subjects who initiated any study procedure for treatment under the current manufacturing Drug Process 2a (DP2a) (Group C), 100% (43/43) reported adverse events (AEs), 83.7% (36/43) of subjects reported treatment-emergent adverse events (TEAEs), and 9.3% (4/43) reported AEs

related to drug product. Also, 76.7% (33/43) reported serious AEs (SAEs), 39.5% (17/43) of subjects reported treatment-emergent SAEs, and 4.7% (2/43) of subjects reported SAEs related to drug product. In the integrated safety analysis, the DP2a safety data pool included 59 subjects who initiated any study procedures for treatment under DP2a from Studies HGB-206, HGB-210, LTF-307 (BLA three-month safety update). 100% (59/59) of subjects reported AEs, 79.7% (47/59) of subjects reported TEAEs, and 10.2% (6/59) of subjects reported Drug Product Related AEs. Additionally, 81.4% (48/59) of subjects reported SAEs, 44.1% (26/59) of subjects reported Treatment-Emergent SAEs, and 3.4% (2/59) reported Drug Product Related SAEs. In the DP2a pool, one subject died after lovo-cel administration; the death was not considered by the investigator to be related to lovo-cel.

10.2 Conclusions and Recommendations

The clinical efficacy data from Study HGB-206 provided adequate statistical evidence for clinical effectiveness of the product. No major safety concern was identified. From the statistical perspective, the clinical efficacy and safety support approval of the product for the proposed indication.