BLA Clinical Review Memorandum

Application Type	BLA
STN	125788/0
CBER Received Date	April 21, 2023
PDUFA Goal Date	December 20, 2023
Division / Office	Division of Clinical Evaluation Hematology/ Office of Clinical Evaluation/ Office of Therapeutic Products
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Megha Kaushal, MD (Safety) Ashley Munchel, MD (Efficacy)
Review Completion Date / Stamped Date	December 8, 2023
Supervisory Concurrence	Nicole Verdun
Applicant	Bluebird bio
Established Name	lovotibeglogene autotemcel
(Proposed) Trade Name	Lyfgenia
Pharmacologic Class	
Formulation(s), including Adjuvants, etc.	Autologous CD34+-enriched population of hematopoietic stem cells transduced with the BB305 lentiviral vector encoding $b^{A\text{-}T87Q}$ globin gene
Dosage Form(s) and Route(s) of Administration	Dosage form: Suspension for infusion Route of administration: Intravenous
Dosing Regimen	Single intravenous dose
Indication(s) and Intended Population(s)	Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs).
Orphan Designated (Yes/No)	Yes

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GLOSSARY

ACS	acute chest syndrome
AE	adverse event
AML	acute myeloid leukemia
BLA	Biologics License Application
BM	bone marrow
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls
FISH-MDS	fluorescence in situ hybridization-myelodysplastic syndrome
FDCA	Federal Food, Drug, and Cosmetic Act
GR	globin response
Hb/HbA/HbS	hemoglobin/hemoglobin A/hemoglobin S
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
IND	Investigational New Drug
IS	integration site
ISA	integration site analysis
ITT	intention to treat
LTFU	long-term follow-up
LVV	lentiviral vector
MDS	myelodysplastic syndrome
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NGS	next-generation sequencing
PB	peripheral blood
PB VCN	vector copy number in peripheral blood
PI	package insert
pRBC	packed red blood cells
PROMIS	Patient Reported Outcomes Measurement Information System
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
sVOE	severe vaso-occlusive events
sVOE-CR	complete resolution of severe vaso-occlusive events
TCD	transcranial doppler
TIA	transient ischemic attack
TP	transplant population
TP-VOE	transplant population for vaso-occlusive events
VCN	vector copy number
VOE	vaso-occlusive event
VOE-CR	complete resolution of vaso-occlusive events
VOE-CR24	complete resolution of vaso-occlusive events at 24 months

1. EXECUTIVE SUMMARY

Sickle cell disease (SCD) is a hereditary blood disorder caused by a point mutation within codon 6 of the hemoglobin (Hb) *β-globin* gene (glutamic acid replaced with valine), which results in the production of an abnormal globin chain (βS-globin). In SCD, hemoglobin S (HbS) forms rigid polymers upon deoxygenation or other conditions of stress. HbS polymerization results in deformation of red blood cells (RBCs) into the characteristic sickle shape, leading to reduced RBC lifespan, chronic hemolytic anemia, and hemolysis. Vaso-occlusive events (VOEs) occur when RBC sickling prevents the free flow of blood for delivery of oxygen and nutrients to end organs. These events can occur in many organs, as acute chest syndrome (ACS), vasculopathy and stroke, splenic or hepatic sequestrations, or VOE-induced priapism. However, VOEs most often occur in the bones, causing pain crises, the hallmark complication of SCD. VOEs are associated with an increased risk of sudden death and cumulative disease progression. Current available therapies include packed red blood cell (pRBC) transfusions, including chronic exchange transfusion, hydroxyurea (HU), L-glutamine, crizanlizumab, voxelotor, and allogeneic hematopoietic stem cell transplantation (HSCT).

Lovotibeglogene autotemcel or lovo-cel consists of an autologous CD34+ cell-enriched population from patients with SCD that contains hematopoietic stem cells transduced with a BB305 lentiviral vector (LVV) encoding the $\beta^{A\text{-}T87Q}$ *globin* gene. $\beta^{A\text{-}T87Q}$ globin is a human βA-globin with a genetically engineered single amino acid change (threonine [T] to glutamine [Q]) at position 87 (T87Q) that sterically inhibits polymerization of HbS.

Data to support the approval of lovo-cel is from Study Hgb-206. This is an ongoing Phase 1/2, open-label, multicenter study evaluating the safety and efficacy of lovo-cel in subjects with SCD. Subjects were assigned to a group (A, B or C) based on the stem cell source and the manufacturing process, which changed during the course of Hgb-206. All subjects on Hgb-206 (groups A, B, and C) who initiated stem cell collection were included in the safety evaluation (N=54). The efficacy evaluation is limited to subjects in group C who underwent apheresis of plerixafor-mobilized peripheral blood (PB) for stem cell collection and received drug product manufactured using process 2a, which reflects the commercial product. The primary efficacy endpoint was complete resolution of VOEs (VOE-CR) between 6 and 18 months following lovo-cel infusion. Subjects with a history of at least four VOEs in the 24 months prior to informed consent were included in the primary efficacy evaluable population (transplant population for vaso-occlusive events [TP-VOE]). Thirty-two subjects met eligibility criteria to be included in the TP-VOE. Of the 32 subjects, 28 achieved VOE-CR (87.5%; 2-sided confidence interval [CI]: 71%, 96.5%). Safety was based on the 54 subjects in groups A, B, and C who received lovo-cel. The most common (>20%) ≥Grade 3 adverse reactions included stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.

There were three deaths. One subject had a sudden death from an acute cardiac event at month 20 following lovo-cel. Two subjects in group A developed acute myeloid leukemia (AML) and subsequently died. One subject in group C developed myelodysplastic syndrome (MDS).

The Applicant has provided substantial evidence of effectiveness and safety based on a single well-controlled clinical investigation providing evidence of clinical benefit, supported by preclinical studies. There are risks with infusion of lovo-cel, including hematologic malignancies, which are described in the label. However, the benefit-risk assessment is favorable with the robust efficacy, and the clinical review team recommends regular approval of lovo-cel for the treatment of patients 12 years of age and older with SCD and a history of VOEs.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1: Demographic Characteristics, All ITT Subjects, Study Hgb-206

Characteristic	Statistic	N=54
Age	-	-
Age at informed consent or assent	median (min, max)	25 (12, 43)
Adult: ≥18 years to ≤50 years	n (%)	37 (82.2)
Pediatric: ≥12 years to <18 years	n (%)	8 (17.8)
Sex	-	-
Male	n (%)	30 (66.7)
Female	n (%)	15 (33.3)
Race	-	-
Asian	n (%)	1 (2.2)
Black/African American	n (%)	43 (95.6)
Not provided	n (%)	1 (2.2)
Ethnicity	-	-
Hispanic	n (%)	1 (2.2)
Not Hispanic	n (%)	42 (93.3)
Not provided	n (%)	2 (4.4)

Source: Adapted from the original BLA Hgb-206 Clinical Study Report p. 139
Abbreviations: n (%)=number of subjects with the specified characteristic, N=number of subjects in the specified group or the total sample.

1.2 Patient Experience Data

The following patient-reported outcomes were assessed as part of the trial:

- Patient Reported Outcomes Measurement Information System (PROMIS)
- Overall health: EuroQoL-5D
- Work productivity: Work Productivity and Activity Impairment Questionnaire-General Health
- Cognitive function: PROMIS Short Form 6a
- Chronic Pain: Analgesic, Anesthetic, and Addiction Clinical Trial Innovations Opportunities and Networks – American Pain Society Taxonomy

Reviewer comment*: An overview of the results is summarized in Section 6.1.11.2. However, given the limitations of quality of life assessments in uncontrolled, open-label trials, these data were not evaluated as part of the application review.*

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	

☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

The *β-globin* gene encodes the β-chains of hemoglobin A (HbA), a heterotetramer comprising two β-globin and two α-globin chains (α2β2) that usually accounts for >95% of the Hb in the blood of children and adults. SCD is a hereditary blood disorder caused by a point mutation within codon 6 of the *β-globin* gene (glutamic acid replaced with valine) and results in the production of an abnormal globin chain (βS-globin). SCD causes RBCs, which are normally disc-shaped and easily flow through blood vessels, to become sickle-shaped and rigid. Sickled RBCs polymerize or clump together. The clumps of misshapen RBCs occlude blood flow through the vessels, blocking delivery of oxygen to organs and tissues. Vaso-occlusion results in recurrent episodes of pain and end organ damage potentially affecting every organ in the body, including the brain, lungs, heart, blood vessels, and kidneys. The abnormally shaped RBCs are more readily destroyed by the body, leading to chronic hemolytic anemia. Patients with SCD also have poor splenic function and therefore are at a higher risk of life-threatening bacterial infections, especially in children. Because of these sequelae, patients with SCD have a 20- to 30-year lower life expectancy than that of the general population.

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

There are currently no approved gene therapies for SCD.

The currently approved disease-modifying agents have been approved and regulated by the Center for Drugs Evaluation and Research. These include HU, L-glutamine, voxelotor, and crizanlizumab.

2.3 Safety and Efficacy of Pharmacologically Related Products

See Section 2.4.

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

Bluebird Bio developed betibeglogene autotemcel (beti-cel; [Zynteglo]), for the treatment of adults and children with transfusion-dependent β-thalassemia. Beti-cel and lovo-cel have identical vectors and the transgene is the same.

With beti-cel, over 90% of subjects achieved transfusion independence that remained durable through last follow-up at 36 months. Most adverse events (AEs) were attributed to busulfan myeloablation. One exception was delayed platelet engraftment and prolonged thrombocytopenia that was attributed to beti-cel. Beti-cel was approved in 2022. There have been no new postmarketing concerns with safety or efficacy that were identified in the original Biologics License Application (BLA) submission.

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

Table 2: Regulatory Milestones Related to the Submission

Regulatory Milestones	Date
1) Pre-IND meeting	November 20, 2013
2) IND submission	March 14, 2014
3) Fast Track designation granted	May 8, 2014
4) Orphan Drug designation granted	February 26, 2014
5) Regenerative Medicine Advanced Therapy granted	October 26, 2017
6) Rare Pediatric Disease designation granted	May 14, 2020
7) BLA 125788/0 submission	April 21, 2023
8) BLA filed	June 20, 2023
9) Action Due Date	December 20, 2023
10) Approval Date	December 8, 2023

Source: FDA
Abbreviations: BLA=biologics license application, IND=investigational new drug.

Summary of Key Meetings

1) October 5, 2018: Type B Regenerative Medicine Advanced Therapy Meeting
   The Sponsor was seeking feedback on the major protocol amendment (version 8) submitted in July 2018. In the protocol amendment, the primary efficacy endpoint was changed to globin response (GR) with the plan of using GR as a surrogate endpoint to seek accelerated approval with the defined clinical benefit of 75% reduction in VOEs in the 24 months following lovo-cel infusion. Key points of discussion are as follows:
   a) FDA did not agree that GR would be an acceptable surrogate endpoint until sufficient data was collected to do a correlation analysis.
   b) FDA recommended resolution of VOEs rather than 75% reduction as a more meaningful clinical benefit.
   c) FDA did not agree with the 40% null hypothesis and requested an updated statistical analysis plan (SAP).
2) April 29, 2020: Type B Regenerative Medicine Advanced Therapy Meeting
   The Sponsor was seeking feedback on the plan to submit a BLA using data from Hgb-206 group C to support accelerated approval with GR as a surrogate endpoint for the clinical benefit of 75% VOE reduction. Key points of discussion are as follows:

a) FDA did not agree that reduction in VOEs would be an acceptable clinical endpoint to correlate with GR and continued to recommend that absence of VOEs represents a more meaningful clinical benefit endpoint. The Sponsor agreed to update the primary efficacy endpoint to complete resolution of severe VOEs (sVOE-CR) for a period of 6 to 18 months following lovo-cel.
b) The Sponsor proposed a new sample size, null hypothesis, and success criteria. FDA requested that a new SAP be submitted with the protocol amendment.

3) December 13, 2021: Type B Meeting
The Sponsor was seeking feedback on version 10 of the protocol submitted in November 2020 in which the primary endpoint was changed from GR to sVOE-CR. Key points of discussion are as follows:
a) FDA recommended changing the primary efficacy endpoint from resolution of sVOEs to resolution of all VOEs requiring visit to a health care facility.
b) FDA requested a revised SAP to address the following feedback:
- FDA recommended that primary efficacy analysis include all subjects who receive drug product, not just those with history of VOEs.
- FDA continued to disagree with the 40% null hypothesis.

4) October 6, 2023: Late-Cycle Meeting
At the time of the BLA submission, the data cutoff was August 11, 2022. At the late-cycle meeting, the Applicant agreed to update the data cutoff to February 13, 2023, for the safety and efficacy analysis.

2.6 Other Relevant Background Information

The Investigational New Drug (IND) was placed on hold on February 16, 2021, when a case of AML and a case of MDS (which later transformed to AML) were reported as possibly related to the drug product. The hold was removed on May 25, 2021, after the mitigation plan was noted to be adequate. The IND was placed on a subsequent partial hold in December 2021 after another case of MDS was reported. Sponsor submitted a complete response to Clinical Hold on April 5, 2022 which was inadequate and the partial hold continued. The hold was removed on December 16, 2022 after the response was deemed adequate.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document according to FDA guidance for electronic submission. The submission consisted of the five modules in the Common Technical Document structure. The modules were adequately organized and integrated to allow the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices and Submission Integrity

The Applicant noted that the study complied with good clinical practices. There were no clinical study conduct or data integrity issues that impacted the clinical review of this submission. Bioresearch Monitoring inspections were issued for three clinical study sites that participated in the conduct of Study CT-AMT-061-02.

The inspections did not reveal significant issues impacting the integrity of the data submitted in support of this application.

3.3 Financial Disclosures

Table 3: Summary of Clinical Study Financial Disclosures

Study Number	Study Title	Disclosure Start Date	Disclosure Cutoff Date
Hgb-205	A Phase 1/2 Open Label Study Evaluating the Safety and Efficacy of Gene Therapy of β- Hemoglobinopathies (Sickle cell anemia and β-Thalassemia major) by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector (LentiGlobin BB305 Drug Product)	June 7, 2013	February 26, 2020 (completion date: February 26, 2019)
Hgb-206	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	August 1, 2014	August 11, 2022
Hgb-210	A Phase 3 Study Evaluating Gene Therapy by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with BB305 Lentiviral Vector in Subjects with Sickle Cell Disease	February 14, 2020	August 1, 2022

Source: Adapted from Financial Certification and Disclosure Form Submitted with original BLA (section 1.3.4)

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 248
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 1

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 1

Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided?

X Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Reviewer comment: *One sub-investigator on studies Hgb-205 and LTF-303 (the predecessor long-term follow-up study to LTF-307) at site 101 left his position at Hospital Necker-Enfants Malades in Paris, France, in August 2017 to join BBB as a full-time employee in September 2017. As a sub-investigator, he received payments from BBB for consulting services from 2014 to 2017. Following his employment with BBB, he received a salary and stock options. The Applicant has adequately disclosed financial interests. The financial interests of this investigator do not affect the integrity of the data presented in this BLA, as the population included in this review only include subjects enrolled on Study Hgb-206, for which this person was not a sub-investigator. Additionally, BBB has confirmed in their statement of financial disclosures that during the conduct of all covered clinical submitted in this BLA, they applied procedures designed to minimize the potential of bias in the data.*

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

The findings below are based on preliminary discussions, such as those at the mid-cycle meeting, with the corresponding reviewer(s) in the relevant discipline(s).

4.1 Chemistry, Manufacturing, and Controls

Lovo-cel consists of an autologous CD34+ cell enriched population containing hematopoietic stem and progenitor cells (HSCs) transduced with a non-replicating lentiviral vector (LVV), referred to as BB305, containing the human $\beta^{A\text{-}T87Q}$-globin transgene sequence. Lovo-cel is supplied frozen in 20 mL fluoro-ethylene-propylene bags as a suspension for intravenous infusion after thawing. Each bag contains 20 mL of a suspension of (b) (4) to 20×10^6 cells/mL. The minimum dose is 3.0×10^6 CD34+ cells/kg of patient weight. Please refer to the Chemistry, Manufacturing, and Controls (CMC) review memo for details.

4.2 Assay Validation

Please refer to the CMC review memo for details.

4.3 Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies were conducted with CD34+ HSCs from SCD patients and showed that erythroid cells derived from BB305 LVV-transduced HSCs produce $\beta^{A\text{-}T87Q}$ globin.

In vivo proof-of-concept studies in immunodeficient mice administered BB305 LVV-transduced CD34+ HSCs obtained from healthy donors displayed bone marrow (BM) engraftment and $\beta^{A\text{-}T87Q}$-globin expression. In vivo proof-of-concept studies were also conducted using transgenic mouse models of SCD, where murine BM cells were transduced with the $\beta^{A\text{-}T87Q}$ HPV436 LVV, a related vector encoding the same transgene, and showed expression of $\beta^{A\text{-}T87Q}$ and correction of the sickling phenotype through 3 months post-transplantation. Please refer to the Pharmacology/Toxicology memo for details.

4.4 Clinical Pharmacology

After infusion of lovo-cel, lentiviral vector copy number in peripheral blood (PB VCN) levels increased rapidly over the first few months before reaching a plateau. At Month 6, the median (min, max) PB VCN level of DP2a product was 1.5 (0.6, 4.6) vc/dg (N=36). PB VCN levels generally remained stable as of the data cutoff date for all studies, although high intersubject variability of PB VCN kinetic profiles were observed.

HbA^{T87Q} generally increased steadily after administration of lovo-cel, and stabilized by approximately Month 6 post-infusion. At Month 6, the median (min, max) level of HbA^{T87Q} was 5.2 (2.6, 8.8) g/dL (N=33) and remained durable at Month 24 with median (min, max) levels of 5.5 (2.4, 9.4) g/dL (N=34). HbA^{T87Q} comprised a median (min, max) 45.7 (26.9, 63.2) (N=34) percent of total nontransfused Hb at Month 24. Expression of Hb^{AT87Q} continued to remain durable through Month 48 (N=10), demonstrating sustained expression of the $\beta^{A\text{-}T87Q}$ protein derived from irreversible integration of the $\beta^{A\text{-}T87Q}$*-globin* gene into long-term HSCs.

The kinetic profile of HbS was similar to that of HbA^{T87Q}. HbS levels increased initially after administration of lovo-cel and stabilized by approximately Month 6 post-infusion. At Month 6, the median (min, max) level of HbS was 5.8 (1.6, 7.3) g/dL (N=33). HbS levels remained stable during the study.

Please refer to the Clinical Pharmacology memo for details.

4.5 Statistical

Please refer to the Statistical Review memo for further details.

4.6 Pharmacovigilance

Please refer to the Office of Biostatistics and Pharmacovigilance review memo for further details.

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

5.1 Review Strategy

The clinical review focused on the Phase 1/2 study that was submitted in Module 5, with review of the Phase 3 study as supportive data.

Reviewer comment: *Dr. Kaushal reviewed the clinical safety portion of this original application and provided guidance throughout the review cycle to Dr. Munchel, the clinical efficacy reviewer.*

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

Documents pertinent to this review were provided in BLA125788/0 and IND 15905, including the overview, analyses datasets, clinical summary, and clinical study reports.

The following materials from the submission were reviewed:

Module	Information
1.6	Meetings
1.14	Labeling
1.18	Proprietary names
5.2	List of Clinical Studies
5.3.5	Reports of efficacy and safety studies
5.3.5.1	Datasets and Case Report Forms

5.3 Table of Studies/Clinical Trials

Table 4: Studies/Clinical Trials of Lovo-Cel

Trial Name	Phase	Group	Stem Cell Source	Manufacturing Process	Number That Initiated Stem Cell Collection	Number Infused With Drug Product	Status
Hgb-205	1	-	BM	0	3	3	Completed
Hgb-206	1/2	A	BM	1	9	7	Ongoing
Hgb-206	1/2	B	BM+PB	1/2	2	2	Ongoing
Hgb-206	1/2	C	PB	2a	43	36	Ongoing
Hgb-210	3	-	PB	2a	16	11	Ongoing
LTF-307	-	-	-	-	45	-	Ongoing

Source: Adapted from the original BLA Summary of Clinical Efficacy pp. 34-35
Abbreviations: BM=bone marrow, PB=peripheral blood.

Reviewer comment: *Lovo-cel product development is the result of three clinical trials and one long-term follow-up (LTFU) study. All trials were single-arm trials in which subjects underwent BM or PB stem cell harvest, received busulfan myeloablation, and then received drug product infusion. There was a change in the manufacturing process as well as stem cell source during Hgb-206. This is reflected by the different groups in Hgb-206.The commercial product will be manufactured from plerixafor-mobilized PB stem cells using manufacturing process 2a. Therefore, the efficacy evaluable group is Hgb-206 group C, while the safety evaluable group is all subjects who initiated stem cell mobilization in Hgb-206. After 24 months, subjects from all clinical trials are encouraged to enroll on the LTFU study, LTF-307, which will follow patients for an additional 13 years for a total of 15 years following lovo-cel infusion. The primary objective of*

LTF-307 is to evaluate long-term safety. The secondary objective is to evaluate durability of response.

5.4 Consultations

No clinical consultations were requested or required during the review of this BLA.

5.4.1 Advisory Committee Meeting

An advisory committee meeting was not convened for this product. The application did not raise significant efficacy concerns that could not be addressed through information in the label; consultative expertise was not required, and no public health concerns arose upon the review of this file. The significant safety concerns were addressed through labeling, and a prior advisory committee meeting (elivaldogene autotemcel [eli-cel; Skysona] and beti-cel products) included the discussions on insertional oncogenesis and hematologic malignancy.

5.4.2 External Consults/Collaborations

Analysis of the potential role of LVV in the development of hematologic malignancy after treatment with LVV-based products is very complex. Therefore, the Agency consulted a multidisciplinary expert to serve as special government employee. The SGE has extensive expertise with stem cell transplantation and the treatment of patients with BM diseases and malignancies, and has a special interest in the molecular basis of hematologic malignancies. The SGE is an active laboratory researcher studying DNA methylation in neoplastic cells, as well as hereditary BM cancers.

The SGE advised the review team on issues such as germline mutation screening for predisposition to malignancy; the utility of baseline BM biopsies; and the specifics of follow-up testing, as well as integration site analysis (ISA) and whole genome sequencing.

5.5 Literature Reviewed

Brunson, A, THM Keegan, H Bang, A Mahajan, S Paulukonis, and T Wun, 2017, Increased risk of leukemia among sickle cell disease patients in California, Blood, 130(13):1597-1599.

Eapen, M, R Brazauskas, MC Walters, F Bernaudin, K Bo-Subait, CD Fitzhugh, JS Hankins, J Kanter, JJ Meerpohl, J Bolaños-Meade, JA Panepinto, D Rondelli, S Shenoy, J Williamson, TL Woolford, E Gluckman, JE Wagner, and JF Tisdale, 2019, Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study, Lancet Haematol, 6(11):e585-e596.

Kanter, J, MC Walters, L Krishnamurti, MY Mapara, JL Kwiatkowski, S Rifkin-Zenenberg, B Aygun, KA Kasow, FJ Pierciey, Jr., M Bonner, A Miller, X Zhang, J Lynch, D Kim, JA Ribeil, M Asmal, S Goyal, AA Thompson, and JF Tisdale, 2022, Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease, N Engl J Med, 386(7):617-628.

Kato, GJ, MH Steinberg, and MT Gladwin, 2017, Intravascular hemolysis and the pathophysiology of sickle cell disease, J Clin Invest, 127(3):750-760.

Ribeil, JA, S Hacein-Bey-Abina, E Payen, A Magnani, M Semeraro, E Magrin, L Caccavelli, B Neven, P Bourget, W El Nemer, P Bartolucci, L Weber, H Puy, JF Meritet, D Grevent, Y

Beuzard, S Chrétien, T Lefebvre, RW Ross, O Negre, G Veres, L Sandler, S Soni, M de Montalembert, S Blanche, P Leboulch, and M Cavazzana, 2017, Gene Therapy in a Patient with Sickle Cell Disease, N Engl J Med, 376(9):848-855.

Seminog, OO, OI Ogunlaja, D Yeates, and MJ Goldacre, 2016, Risk of individual malignant neoplasms in patients with sickle cell disease: English national record linkage study, J R Soc Med, 109(8):303-309.

Darbari DS, Liljencrantz J, Ikechi A, et al. Pain and opioid use after reversal of sickle cell disease following HLA-matched sibling haematopoietic stem cell transplant. Br J Haematol. 2019;184(4):690-693.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1: Hgb-206

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 (NCT02140554)

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to evaluate the efficacy of treatment with lovo-cel in subjects with severe SCD.

The secondary objective was to evaluate the safety of treatment with lovo-cel in subjects with severe SCD.

6.1.2 Design Overview

Hgb-206 was a nonrandomized, open-label, multisite, single-dose, Phase 1/2 study in adults and adolescents with severe SCD. Subjects were followed for 24 months on Hgb-206 and then encouraged to enroll in LTF-307, an LTFU study that monitors safety and efficacy of the treatment for an additional 13 years

6.1.3 Population

Key Inclusion Criteria:

- SCD (β^S/β^S, β^S/β^+ thalassemia, β^S/β^0 thalassemia) with at least 4 VOEs requiring medical evaluation in the 24 months prior to signing informed consent
- Age >12 years of age to ≤50 years of age
- Either history of HU failure (defined as >1 VOE or ≥1 ACS after HU had been prescribed for 6 months) or history of intolerance to HU per the investigator's judgement

Key Exclusion Criteria:

- Positive for human immunodeficiency virus type 1 or 2, hepatitis B, hepatitis C, or human T-lymphotrophic virus 1 or 2
- Clinically significant infection

- History of severe cerebral vasculopathy defined by history of overt ischemic or hemorrhagic stroke; abnormal transcranial dopplers (TCD) (>200 cm/sec) requiring chronic transfusion; occlusion or stenosis in the circle of Willis; or presence of Moyamoya disease. Subjects with radiologic evidence of silent infarction in the absence of any of the above were eligible
- If under 18 years of age, could not have a willing, matched human leukocyte antigen-identical sibling hematopoietic cell donor available
- Baseline organ functions
  - Oxygen saturation <90% without supplemental oxygen
  - Carbon monoxide diffusing capacity <50% in the absence of infection
  - Left ventricular ejection fraction <45% by echocardiogram
  - Clinically significant pulmonary hypertension
  - Estimated glomerular filtration rate <70 m/min/1.73 m^2
  - Advanced liver disease defined as any of the following:
    - Persistent aspartate transaminase, alanine transaminase or direct bilirubin >3 times the upper limit of normal
    - Baseline prothrombin time or partial thromboplastin time >1.5× upper limit of normal
    - Magnetic resonance imaging (MRI) of liver demonstrating clear evidence of cirrhosis
    - MRI suggestive of active hepatitis, significant fibrosis; inconclusive evidence of cirrhosis or liver iron content ≥15 mg/g requiring liver biopsy in subjects ≥18 years of age. If <18 years of age, the MRI was exclusionary unless the investigator concluded a liver biopsy may provide additional data and would be safe to perform
- For subjects with history of iron overload or serum ferritin levels >1,000 ng/mL, a cardiac MRI was required. Cardiac $T2^*$<10 ms resulted in exclusion
- Contraindications to plerixafor or busulfan
- Unable to receive RBC transfusion
- Subjects needing therapeutic anticoagulation treatment from conditioning through platelet engraftment
- Prior or current malignancy or immunodeficiency, except previously treated, non-life-threatening, cured tumors
- Immediate family member with known or suspected familial cancer syndrome
- Prior allogeneic transplant
- Prior gene therapy

Reviewer comment:

- *Although subjects could have any of the following sickle cell genotypes, homozygous β^S/β^S, β^S/β^+ thalassemia or β^S/β^0 thalassemia, all subjects in the efficacy evaluable group were homozygous β^S/β^S. Given the similar pathophysiology and demographics, we would expect similar efficacy and safety profiles regardless of the underlying genotype.*
- *In a protocol amendment in July 2018, the inclusion/exclusion criteria were changed to exclude subjects with history of cerebral vasculopathy and overt stroke. Five subjects with history of overt stroke were enrolled prior to this change. Four did not have history of VOEs. Those four are not included in the primary efficacy analysis but are included in*

the secondary endpoints not related to VOE resolution. See Section 6.1.11.2 for outcomes in subjects with history of stroke.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Preparation for mobilization, apheresis, and conditioning:

- All subjects were placed on a pRBC transfusion regimen for at least 60 days prior to mobilization and continuing through the start of conditioning to minimize VOEs. The transfusion goals were to target Hb of 10 g/dL prior to mobilization and 8 to 10 g/dL prior to conditioning, as well as to not exceed 12 g/dL and an HbS trough of <30%.
- The following medications were discontinued prior to mobilization and/or conditioning:
  - Hydroxyurea: HU was discontinued at least 30 days prior to mobilization. It could be restarted between completion of harvest and conditioning but was stopped again at least 2 days before conditioning. HU may be myelosuppressive and interfere with mobilization and engraftment. Additionally, HU would interfere with efficacy evaluation.
  - Disease-modifying agents (i.e., voxelotor, crizanlizumab, L-glutamine) were stopped at least 7 days prior to mobilization and conditioning so as to not interfere with efficacy evaluation.
  - Iron chelation: Iron chelation was discontinued at least 7 days prior to mobilization. It could be restarted after completion of harvest but was stopped again at least 7 days before conditioning and not restarted until at least 3 months post infusion. Iron chelators can be myelosuppressive and interfere with mobilization and engraftment.
  - Antiretrovirals: Antiretrovirals were discontinued at least 30 days prior to mobilization. Antiretrovirals can theoretically interfere with transduction and integration of the LVV.

Mobilization and apheresis:

- Plerixafor: A dose of 0.24 mg/kg was administered 4 to 6 hours prior to the start of apheresis each day.
- Platelet goal: Platelet count of ≥100×10^9/L prior to plerixafor administration on the first day of each cycle of apheresis, and >75×10^9/L prior to administration of plerixafor each day if subsequent days of apheresis were required.
- Aspirin: It was recommended that subjects receive a dose of aspirin (80 to 325 mg) 12 to 30 hours prior to initiation of apheresis.
- Stem cell collection: A goal of collecting ≥16.5×10^6 CD34+ cells/kg was achieved. A total of 1.5×10^6 cells/kg were cryopreserved for rescue. The rest was sent for manufacturing of the drug product. Subjects without adequate cell collection underwent additional mobilization cycles; each cycle was separated by at least 14 days.

Myeloablative conditioning and infusion of lovo-cel:

- Busulfan 3.2 mg/kg/day or 0.8 mg/kg every 6 hours was administered intravenously for 4 consecutive days. For subjects <35 kg, the 6 hour dosing was preferred. The busulfan was adjusted to maintain area under the curve goal of 1,250 µM x min (range 1,100 to 1,350 µM x min) for a 6-hour dosing regimen, or 5,000 µM x min (range 4,400 to 5,400 µM x min) for daily dosing.

- All subjects received antiseizure prophylaxis starting at least 12 hours before initiating busulfan. Phenytoin was not used due to its induction of cytochrome P450 and resultant increase in clearance of busulfan.
- There was a minimum washout period of 48 hours between the last dose of busulfan and administration of lovo-cel.
- Minimum lovo-cel dose was $\geq 3 \times 10^6$ transduced cells/kg with no maximum. All transduced cells were infused.

6.1.5 Directions for Use

Lovo-cel is given via intravenous infusion at least 48 hours after the last dose of busulfan to allow for an adequate washout period. Infuse each bag of lovo-cel over a period of less than 30 minutes. If more than one infusion bag is provided, administer the contents of one infusion bag completely before proceeding to thaw and infuse the contents of the next bag. Flush the infusion bag and tubing with at least 50mL of 0.9% sodium chloride solution to ensure as many cells as possible are infused into the patient.

6.1.6 Sites and Centers

Table 5: Sites and Centers, Study Hgb-206

Country	Site	Site #
France	Paris, France	101
United States	Children's Hospital of Philadelphia Philadelphia, PA	103
United States	UCSF Benioff Children's Hospital Oakland, CA	104
United States	Ann & Robert H Lurie Children's Hospital Chicago, IL	110
United States	Medical University of South Carolina Charleston, SC	113
United States	National Institutes of Health Bethesda, MD	114

Source: Adapted from BLA submission List of Clinical Investigator Contact Information (section 1.3.4)

Reviewer comment: *The only site outside of the United States, Site 101, did not enroll subjects on Hgb-206. Therefore, the efficacy and safety populations analyzed in this BLA include subjects exclusively from the United States.*

6.1.7 Surveillance/Monitoring

An independent data monitoring committee oversaw the safety of all three treatment trials and the LTFU study.

Per protocol, all subjects were evaluated with physical exam and laboratory testing monthly through month 6 and then every 3 months through month 24 following lovo-cel infusion. Bone marrow biopsy, brain MRI/MRA (and TCD is less than 16 years of age), and pulmonary function tests were performed at month 12 and 24. Cardiac MRI, liver MRI, echocardiogram and bone mineral density evaluations were done at month 24. Additional evaluations were performed as clinically indicated.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was complete resolution of adjudicated VOEs between 6 and 18 months following lovo-cel infusion.

VOEs were defined and classified as follows:

- Protocol VOE comprised any of the following:
  - Episode of acute pain with no medically determined cause other than a VOE lasting more than 2 hours and requiring care at a medical facility
  - ACS defined by pneumonia-like symptoms and the presence of a new pulmonary infiltrate and requiring oxygen treatment and/or blood transfusion
  - Acute hepatic sequestration defined by sudden increase in liver size associated with pain in the right upper quadrant; abnormal liver function tests not due to biliary disease and a reduction in Hb concentration by at least 2 g/dL below baseline
  - Acute splenic sequestration defined by sudden increase in spleen size and a reduction in Hb concentration by at least 2 g/dL below baseline
  - Acute priapism requiring care at a medical facility
- Protocol sVOE comprised either of the following:
  - Protocol VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours, requiring intravenous medications at each visit ***OR***
  - Acute priapism requiring any level medical attention (all protocol VOEs of acute priapism met definition of sVOE)
- Adjudicated VOE: All protocol VOEs and sVOEs were reviewed by an independent adjudication committee to confirm they met the definition of protocol VOE.
- Investigator VOE: any VOE recognized by the investigator regardless of the duration, severity, treatment, or need for medical facility visit. Investigator VOEs were not used for any efficacy analysis.

Key secondary efficacy endpoints were:

- Complete resolution of sVOE (sVOE-CR) between 6 and 18 months after lovo-cel
- Globin Response (GR) defined as meeting both following criteria for a continuous period of 6 months after lovo-cel
  - Weighted average nontransfused total Hb increase of $\geq$3 g/dL compared to baseline or $\geq$10 g/dL. Nontransfused Hb was calculated as total g/dL of HbS+HbF+HbA_2+HbA^{T87Q}
  - Weighted average HbA^{T87Q} percentage of nontransfused total Hb ≥30%. Weighted average HbA^{T87Q} percentage was calculated by dividing HbA^{T87Q} (g/dL) by nontransfused total Hb (g/dL)

Additional secondary endpoints were:

- VOE-CR, sVOE-CR, and GR at 24 months
- Change in hemolytic parameters
- Chronic complications including renal, cardiac, and pulmonary function
- Quality of life/patient-reported outcomes

Reviewer comment: *The primary efficacy endpoint of Hgb-206 was changed multiple times. The changes are summarized below.*

- *Versions 1 to 7 (December 2012 to July 2018):The primary efficacy endpoint was comparing frequency of sickle-cell-related clinical events in the 2 years prior to signing informed consent to the 2 years after gene therapy.*
- *Version 8 (July 2018): The primary efficacy endpoint was changed to GR, as the Sponsor was proposing GR as a surrogate endpoint to seek accelerated approval with GR being a surrogate for the clinical benefit of 75% reduction in annualized VOEs.*
- *Version 10 (November 2020): The primary efficacy endpoint was changed from GR to sVOE-CR.*
- *Version 12 (June 2022): The primary efficacy endpoint was changed from sVOE-CR to VOE-CR.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

The SAP defines a null hypothesis of 40% for the primary efficacy endpoint. Using that null hypothesis, a sample size of 35 subjects was calculated to achieve greater than 99% power. Separate power calculations were performed for the key secondary endpoints of sVOE-CR and GR. The null hypothesis was 50% for sVOE-CR with sample size calculation of 35. The null hypothesis was 40% for GR with a sample size calculation of 41.

Reviewer comment: *The null hypothesis of 40% was first defined in version 8 (July 2018) of the protocol when the primary endpoint was changed to GR. At the Type B meeting in October 2018, FDA clearly stated they did not agree that achieving that threshold would result in clinical benefit of VOEs. Additionally, FDA stated there were "immediate toxicities from the conditioning regimen, potential limitations from the conditioning regimen on the ability to avail future stem cell transplant options, and potential long-term risks associated with gene therapy; a greater magnitude of clinical benefit compared to available therapies will be needed to justify risk-benefit ratio." FDA has remained consistent in that feedback, disagreeing with the null hypothesis at each of the meetings held between October 2018 and December 2021. At the December 2021 Type B meeting, the following feedback was given to the Sponsor:*

- *FDA recommended the entire population be used for the primary endpoint analysis and not just subjects who had a history of ≥4 VOEs.*
- *FDA disagreed with the 40% null hypothesis, as there was no clear justification for that number.*
- *As the Sponsor proposed lovo-cel as a potentially "curative" therapy, FDA recommended the Sponsor provide data from allogeneic stem cell transplant, the only curative option for SCD, to better contextualize the proposed null hypothesis.*

The Sponsor submitted a revised SAP in June 2022. The Sponsor did not incorporate FDA feedback into the revised SAP. The SAP defines the primary efficacy population as those with history of at least 4 protocol VOEs in the 24 months prior to informed consent rather than including the entire treated population and defines the null hypothesis of 40% for the primary efficacy endpoint. The Sponsor also did not provide literature to support the use of 40% for the null hypothesis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Hgb-206 Population:

- Intention to treat (ITT; N=54): subjects in groups A, B and C who signed informed consent and initiated the process of stem cell collection. This was the population used for safety evaluation.
- Transplant population (TP; n=45): subjects in groups A, B and C who were infused with drug product.
- TP group C (N=36): Subjects in group C who received drug product. This is the population used for secondary endpoints not related to VOE resolution.
- TP-VOE group C (N=32): Subjects in group C who had at least 4 protocol VOEs in the 24 months prior to informed consent. This is the population used for analysis of VOE-CR and sVOE-CR.

Nine subjects treated on Hgb-206 discontinued after stem cell collection but prior to conditioning:

- Two subjects in group A. One subject withdrew consent. The other subject was discontinued by the investigator due to poor yield from multiple BM harvests.
- Seven subjects in group C:
  - Four subjects withdrew consent
  - One failed to mobilize
  - Two subjects were discontinued by the investigator:
    - One for behavior issues
    - One for central line infection and poor mobilization

6.1.10.1.1 Demographics

Table 6: Demographic Characteristics, Study Hgb-206

Characteristic	Statistic	ITT (N=54)	TP Group C (N=36)	TP-VOE Group C (N=32)
Age at informed consent or assent (years)	median	25	24	25
Age at informed consent or assent (years)	min, max	12, 43	12, 38	12, 38
Age at informed consent or assent (category)	-	-	-	-
≥18 years to ≤50 years	n (%)	45 (83.3)	28 (77.8)	24 (75)
≥12 years to <18 years	n (%)	9 (16.7)	8 (22.2)	8 (25)
Sex	-	-	-	-
Male	n (%)	34 (63)	22 (61.1)	20 (62.5)
Female	n (%)	20 (37)	14 (38.9)	12 (37.5)
Race	-	-	-	-
Asian	n (%)	1 (1.9)	0	0
Black/African American	n (%)	48 (88.9)	35 (97.2)	31 (96.9)
Not provided	n (%)	2 (3.7)	1 (2.8)	1 (3.1)

Characteristic	Statistic	ITT (N=54)	TP Group C (N=36)	TP-VOE Group C (N=32)
Ethnicity	-	-	-	-
Hispanic	n (%)	2 (3.7)	1 (2.8)	1 (3.1)
Not Hispanic	n (%)	50 (92.6)	33 (91.7)	29 (90.6)
Not provided	n (%)	2 (3.7)	2 (5.6)	2 (6.3)

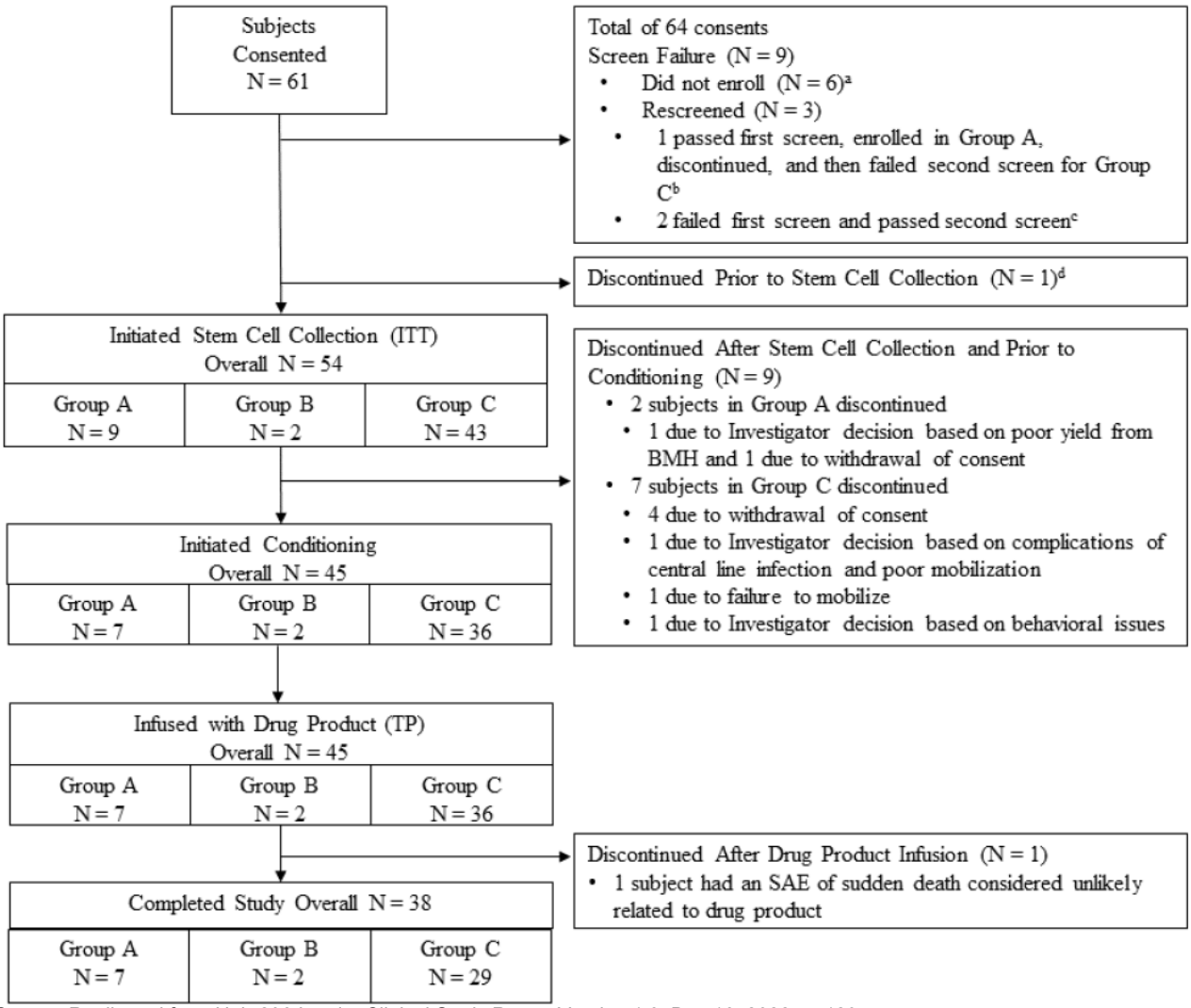
Source: Adapted from the original BLA Hgb-206 Clinical Study Report p. 139
Abbreviations: BLA=biologics license application, N=number of subjects in the specified group or the total sample, TP=transplant population, TPVOE=transplant population with history of ≥4 vaso-occlusive events in the 24 months prior to informed consent.

Reviewer comment:

- *More adults were treated than adolescents because treatment of adolescents was performed in a staggered fashion. There is an ongoing Phase 3 trial, Hgb-210, enrolling subjects ≥2 years of age, which will provide more data on the pediatric population.*
- *The race and ethnicity of the treated population reflects the epidemiology of SCD.*
- *More men were treated than women. The reason for this difference is not clear. Given the small sample size, it was not possible to make any conclusions regarding difference in response between men and women. See Section 6.1.11.3 for details.*

6.1.10.1.3 Subject Disposition

Figure 1: Subject Disposition, Study Hgb-206



Source: Replicated from Hgb-206 Interim Clinical Study Report Version 1.0, Dec 16, 2022, p. 129
Abbreviations: BMH=bone marrow harvest, ITT=intention to treat, N=number of subjects in the specified group or the total sample, SAE=serious adverse event, TP= transplant population.

6.1.11 Efficacy Analyses

The 36 subjects in Hgb-206 TP group C underwent mobilization with plerixafor followed by apheresis for PB stem cell collection. They all received myeloablative conditioning with busulfan followed by intravenous infusion of lovo-cel with a median (min, max) dose of 6.1 (3, 14)×10^6 CD34+ cells/kg.

6.1.11.1 Analyses of Primary and Key Secondary Endpoint(s)

Resolution of VOEs

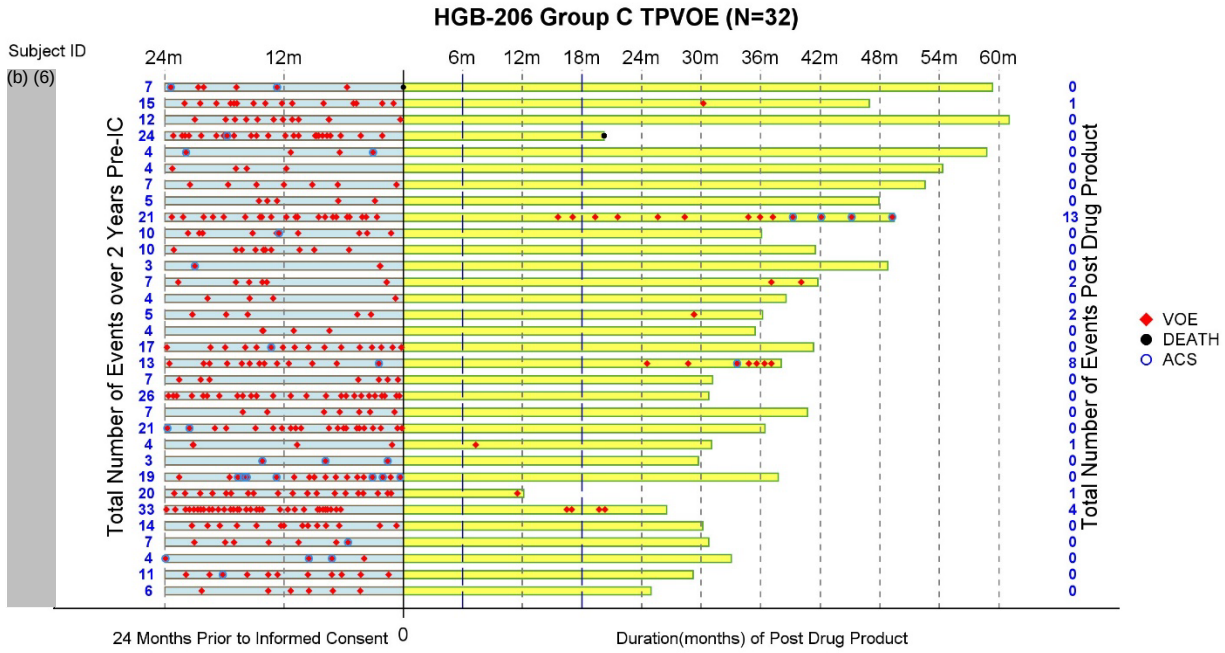
Thirty-two of 36 subjects on Hgb-206 group C (TP-VOE) met the criteria of having at least 4 Protocol VOEs in the 24 months prior to signing informed consent and were included in the evaluation for the primary efficacy endpoint, VOE-CR, and the key secondary efficacy endpoint, sVOE-CR.

Table 7: Summary of VOE Efficacy Outcomes

Efficacy Endpoint	Results N=32
VOE-CR	-
n (%)	28 (87.5)
[95% CI]	71.0, 96.5
sVOE-CR	-
n (%)	30 (93.8)
[95% CI]	79.2, 99.2

Source: FDA analysis
Abbreviations: CI=confidence interval, n (%)=number of subjects with the specified characteristic, N=number of subjects in the specified group, or the total sample, VOE-CR=complete resolution of vaso-occlusive events, sVOE-CR=complete resolution of severe vaso-occlusive events.

Figure 2: HGB-206, Adjudicated VOEs in Group C TPVOE (N=32)



Source: FDA analysis based on data cutoff February 13, 2023
Abbreviations: ACS= acute chest syndrome, VOE= vaso-occlusive event.

Reviewer comment:

- *Figure 2 plots Adjudicated VOEs pre and post lovo-cel infusion. Two subjects have only 3 Adjudicated VOEs in the 24 months prior but are included in the TP-VOE because*

each had 4 Protocol VOEs. As defined by the SAP, the TP-VOE evaluable population included subjects with at least 4 Protocol VOEs in the 24 months prior to signing informed consent regardless of adjudication. Since the primary efficacy endpoint was based on resolution of Adjudicated VOEs, we performed a sensitivity analysis excluding the two subjects who had less than 4 Adjudicated VOEs in the 24 months prior to signing informed consent. Twenty-six of 30 subjects achieved VOE-CR (86.7%; 2-sided CI: 69.3%, 96.2%). *There is no significant difference in primary efficacy outcome using history of Adjudicated VOEs versus history of Protocol VOEs to define TP-VOE.*

- *While FDA never agreed to the null hypothesis of 40%, the percentage of subjects who achieved VOE-CR was well above the lower bound of the CI. Therefore, lovo-cel is considered to have demonstrated clinical efficacy.*

- *The four subjects in TP but not in TP-VOE were enrolled prior to the change in inclusion/exclusion criteria and primary efficacy endpoint. All four subjects were enrolled due to history of overt stroke and did not have a history of VOEs prior to lovo-cel. None of the four subjects experienced a VOE between 6 and 18 months following lovo-cel.*

Globin Response (GR)

All 36 subjects in Hgb-206 TP group C were included in the GR evaluation. Thirty-one subjects (86%; 2-sided CI: 70.5%, 95.3%) achieved GR. Other than the subject who died at Month 20, all subjects that had achieved GR maintained it at 24 months. One subject failed to maintain GR in LTFU. This subject experienced Grade 3 gallstone pancreatitis requiring laparoscopic cholecystectomy at Month 35. The subject received an exchange transfusion followed by a straight transfusion for supportive care prior to surgery. The subject recovered from that event and has not required any additional transfusions. At his 42-month follow-up, 6 months following the event of pancreatitis, his nontransfused total Hb was 14.2 g/dL, and nontransfused HbA^{T87Q} was 48.6%.

Table 8: Subjects Who Failed to Achieve Globin Response

SUBJ ID	Age	Sex	Weighted Hb A^{T87Q} Percentage ≥30%	Weighted Non-transfused Total Hb >10 g/dL or 3 g/dL Above Baseline	Month 12 VCN
(b) (6)	25	F	No	No	0.52
	19	F	-	No	5.5
	38	F	-	No	1
	25	M	No	-	0.4
	12	M	-	No	3.3

Source: FDA analysis
Abbreviation: VCN=vector copy number.

Reviewer comment:

- *There is no correlation between weighted HbA^{T87Q} percentage and weighted non-transfused total Hb.*
- *The failure to achieve HbA^{T87Q} >30% seems to be related to vector copy number (VCN) as both subjects who failed to achieve a HbA^{T87Q} >30% had among the lowest VCN of all subjects treated in Hgb-206.*
- *There is no clear risk for failure to achieve an increase in non-transfused total Hb.*

- *Two of the subjects who failed to have an increase in total Hb (b) (6) have two-gene α-thalassemia deletion and developed dyserythropoeisis following lovo-cel infusion. Subject (b) (6) has been diagnosed with MDS, and Subject (b) (6) developed severe transfusion-dependent anemia following lovo-cel infusion. See Section 6.1.12.5 for details regarding these two subjects.*
- *The etiology of persistent anemia in the other two subjects is not clear. Subject (b) (6) had no baseline Hb documented. This subject's total Hb stabilized between 8 to 9 g/dL following lovo-cel. Subject (b) (6) had a baseline Hb of 8.2 g/dL. This subject's post-lovo-cel Hb stablized between 9 to 10 g/dL, higher than baseline but not high enough to achieve GR. Neither have any known risk factors for anemia. Neither have evidence of dyserythropoeisis or MDS.*

Table 9: Relationship Between VOE-CR and GR

SUBJ ID	Age (Years)	Sex	Achieved VOE-CR	Weighted Hb A^{T87Q} Percentage ≥30%	Non-transfused Total Hb >10 g/dL or 3 g/dL Above Baseline
(b) (6)	25	F	No	No	No
	19	F	No	-	No
	27	F	No	-	-
	30	F	No	-	-
	38	F	-	-	No
	25	M	-	No	-
	12	M	-	-	No

Source: FDA analysis
Abbreviations: GR=globin response, VOE-CR=complete resolution of vaso-occlusive events.

Reviewer comment: *There is no correlation between VOE-CR and either parameter of GR. GR cannot be used as a surrogate endpoint for clinical benefit of lovo-cel. This is further exemplified by the fact that five subjects developed adjudicated VOEs after 24 months despite maintaining GR. See Section 6.1.11.5.*

6.1.11.2 Analyses of Secondary Endpoints

VOE-CR and sVOE-CR at 24 Months

Table 10: VOE-CR and sVOE-CR at 24 Months Following Lovo-cel

Efficacy Endpoint	Result (N=32)
VOE-CR24	-
n (%)	27 (84.4)
[95% CI]	67.2, 94.7
sVOE-CR24	-
n (%)	29 (90.6)
[95% CI]	75.0, 98.0

Source: FDA analysis
Abbreviations: CI=confidence interval, n (%)=number of subjects with the specified characteristic, N=number of subjects in the specified group, or the total sample, VOE-CR24=complete resolution of vaso-occlusive events at 24 months, sVOE-CR24=complete resolution of severe vaso-occlusive events at 24 months.

Reviewer comment: *Twenty-seven of 28 subjects who achieved VOE-CR and sVOE-CR at 18 months maintained VOE-CR between 18 and 24 months. The one failure was due to death from an acute cardiac event at Month 20 following lovo-cel. At the time of death, that subject had not experienced any VOEs post infusion. While no additional subjects developed VOEs between 18*

and 24 months, 5 subjects experienced their first adjudicated VOE after 24 months. See Section 6.1.11.5 for more details.

Hemolysis

Table 11: Subjects With Abnormal Hemolytic Parameters at Baseline and Following Lovo-cel Infusion

Time Following Lovo-cel Infusion	Elevated Indirect Bilirubin	Elevated LDH	Elevated Reticulocyte Count	Low Haptoglobin
Baseline	-	-	-	-
N	36	34	36	32
n (%)	35 (97.2)	33 (97)	36 (100%)	24 (75)
12 months	-	-	-	-
N	35	34	35	33
n (%)	25 (71.4)	25 (73.5)	32 (91)	13 (39.3)
24 months	-	-	-	-
N	29	28	33	30
n (%)	22 (75.8)	22 (78.5)	25 (75)	15/30 (50)

Source: FDA analysis
Abbreviations: LDH=lactate dehydrogenase, n (%)=number of subjects with the specified characteristic, N=number of subjects in the specified group or the total sample.

Reviewer comment: *A hallmark finding in patients with sickle cell anemia is chronic hemolysis. Laboratory markers of hemolysis include elevated serum levels of indirect bilirubin, reticulocyte count, and lactate dehydrogenase, and a low serum haptoglobin. Chronic hemolysis has been implicated in contributing to vasculopathy and end organ damage. Evidence has shown the more abnormal a patient's hemolytic markers are, the higher the risk of pulmonary hypertension, cerebrovascular disease, leg ulcers, priapism, and sickle nephropathy (Kato et al. 2017).*

In Study Hgb-206, most subjects continued to have laboratory evidence of hemolysis at 24 months following lovo-cel infusion. The long term clinical sequela of ongoing laboratory evidence of hemolysis in the setting of a patient who has received lovo-cel is unknown.

Chronic Complications Assessment

During the follow-up assessments, renal, cardiac, and pulmonary function were evaluated using estimated glomerular filtration rate, pulmonary function tests, echocardiogram, and six-minute walk test. Renal, cardiac, and pulmonary function remained stable across the population following lovo-cel infusion.

Reviewer comment: *The majority of subjects had less than 3 years of follow-up. Given the short duration of follow-up, we cannot make any conclusions on the impact of lovo-cel in slowing or preventing end-organ dysfunction.*

Quality of Life

PROMIS

The Applicant included patient-reported quality of life assessments as both secondary and exploratory endpoints. The results of the questionnaires showed stable to slightly improved outcomes in pain intensity, fatigue, and physical functioning. Anxiety, depression, and sleep disturbances remained unchanged.

Chronic Pain

At baseline and every 6 months following infusion, subjects were asked if they had “ongoing sickle-cell-related pain most days over the past 6 months.” Eighteen out of 21 subjects (85.6%) answered “yes” prior to lovo-cel infusion. Nine out of 33 subjects (27%) continued to answer “yes” at 18 or 24 months following lovo-cel infusion, using the most recent timepoint at which they were asked. Chronic pain is likely due to cumulative musculoskeletal damage from repeated episodes of vaso-occlusion resulting in ischemia/reperfusion injury to bone and surrounding tissues. As such, the Applicant stated chronic pain was not expected to resolve with lovo-cel, just as one should not expect reversal of end-organ damage following lovo-cel.

Reviewer comment: *This is a brief overview of the data provided by the Applicant in the BLA submission. Given the limitations of quality of life assessments in uncontrolled, open-label trials, these data were not evaluated as part of the clinical review and not included in the label.*

6.1.11.3 Subpopulation Analyses

Male/Female

Of the 32 subjects in the TP-VOE group, 12 were female (37.5%). All four subjects that failed VOE-CR were female. Therefore, the VOE-CR in females was 8/12 (66.6%).

Reviewer comment: *Per the FDA statistical review team, the sample size is too small to draw conclusions regarding a differential treatment effect between female and male subjects. The Applicant stated that subgroup analyses were performed but no meaningful differences were observed in key drug product characteristics, pharmacodynamic parameters, or clinical outcomes. The Applicant has been unable to identify any drug-related characteristics or underlying gender-related SCD characteristics to explain any potential differences.*

Adolescent/Adult

Eight subjects were between 12 and 18 years of age at the time of treatment. No significant difference in response was noted between adults and adolescents. All adolescent subjects met VOE-CR. One 12-year-old male subject failed GR. This is one of the subjects discussed above with two-gene deletion α-thalassemia and dyserythropoeisis.

Reviewer comment: *We will obtain more pediatric data from Hgb-210, the ongoing Phase 3 trial enrolling subjects 2 years of age and older.*

6.1.11.4 Dropouts and/or Discontinuations

The only subject in Hgb-206 group C who discontinued the study after receiving lovo-cel had sudden cardiac death at Month 20 following lovo-cel infusion.

6.1.11.5 Exploratory and Post Hoc Analyses

Long-Term Follow-up of Subjects Who Failed VOE-CR

The outcome of the four subjects who failed VOE-CR is summarized below.

- Subject (b) (6) had a significant reduction in VOEs after lovo-cel. This subject experienced 4 VOEs between month 6 and 27 following lovo-cel compared to 33 VOEs in the 24 months prior to signing informed consent.

- Subject (b) (6) has 50 months of follow-up and has experienced a total of 13 VOEs following lovo-cel infusion, 5 of which were severe. This subject has had no significant VOE-free periods.

- Subject (b) (6) became transfusion dependent following lovo-cel treatment. While this subject has experienced only one VOE following treatment with lovo-cel, we cannot conclude if the absence of ongoing VOEs is due to a drug product effect or chronic transfusion therapy.

- Subject (b) (6) experienced their first VOE at 12 months following lovo-cel infusion but only has 12 months follow-up. We cannot make any conclusion about VOE reduction following lovo-cel at this time.

Durability of Response

Table 12: Subjects With First Adjudicated VOEs After 24 Months

SUBJ ID	Age	Sex	Timing of First VOE Following Lovo-cel (Month)	Hb A^{T87Q} at Last Follow-Up (%)	VCN at Most Last Follow-Up (c/dg)
(b) (6)	18	M	24	56.1	2
	12	F	29	48	1.72
	26	M	30	37.6	0.95
	12	M	37	37.2	1.21
	21	M	46	40.2	0.94

Source: FDA analysis
Abbreviations: VCN=vector copy number, VOE=vaso-occlusive event.
a. Subject is included in Group C TP but not TP-VOE

Five subjects experienced their first adjudicated VOE at least 24 months after infusion of lovo-cel. Four of the subjects were included in TP-VOE and achieved the primary endpoint of VOE-CR. One subject was in TP but not TP-VOE, as this subject did not have a history of VOEs prior to lovo-cel, but did experience an adjudicated pain crisis 46 months after lovo-cel infusion.

Reviewer comment:

- *Subjects can develop VOEs even after long periods of being VOE-free.*

- *Durability of response is continuing to be evaluated as a secondary outcome in the long-term follow-up study, LTF-307.*

- *As stated above, there is no relationship between GR and VOE-resolution. VOEs occurred despite all subjects maintaining GR and good VCN.*

Efficacy Analysis Using Unadjudicated VOEs Rather Than Adjudicated VOEs

Four subjects who met criteria for VOE-CR and VOE-CR24 experienced unadjudicated VOEs following lovo-cel infusion, one of the events occurred during the primary efficacy evaluable period at month 12. Three of the four went on to have Adjudicated VOEs after 24 months. The

fourth subject did not experience any Adjudicated VOEs following lovo-cel infusion but had five unadjudicated episodes of priapism reported between 36 and 42 months and required a referral to a urologist. In all four subjects, the events were not adjudicated because either the subject did not seek medical care at the time of the acute event or sought medical care but did not receive intravenous pain medications.

Reviewer comment*:*

- *The efficacy analysis using Unadjudicated VOEs is:*
    - *VOE-CR: decreases to 84.3% (27/32)*
    - *VOE-CR24: decreases to 75% (24/32)*
- *The limitations of using Adjudicated VOEs in the efficacy analysis are:*
    - *Because a subject had to seek medical care at the time of the event for the event to meet criteria for an Adjudicated VOE, VOEs managed at home are not captured in the efficacy data. Patients with SCD often attempt to manage pain, priapism, and other mild events at home.*
    - *Crises that do not require medical attention or intravenous pain medications are clinically significant as they contribute to poor quality of life, as well as long-term end-organ dysfunction.*
- *While there are limitations, it is necessary to use Adjudicated VOEs in the context of a clinical trial to limit subjectivity and inaccuracy that innately results from retrospective reporting and provide a system by which results can be validated.*

Effect of Lovo-cel on Specific Types of VOE

Neurologic Events

Prior to the change in primary efficacy endpoint and inclusion/exclusion criteria discussed above, five subjects with a history of stroke were treated (one in the TP-VOE group and four not in the TP-VOE group). All were ≥18 years of age. Four were on chronic transfusion therapy prior to lovo-cel infusion. At 44 to 60 months follow-up, all subjects remained transfusion-independent without recurrent stroke.

One subject (b) (6) with no prior history of stroke or vasculopathy, experienced a Grade 1 non-serious adverse event (SAE) of transient ischemic attack (TIA) that occurred and resolved on Day 18. There were no other reports of neurologic events in any subject following lovo-cel infusion.

All subjects underwent brain MRI/magnetic resonance angiography (MRA) prior to treatment and at Months 12 and 24 post lovo-cel to evaluate for ischemic/hemorrhagic stroke and vasculopathy. Subjects under 16 years of age also had serial TCDs. Per the Applicant, all subjects had stable MRI/MRA and TCD results following lovo-cel infusion. MRI/MRA and TCD reports were not submitted as part of the BLA to validate that statement.

Acute Chest Syndrome

ACS events are captured in Figure 2 by red and blue circles. Fourteen subjects in TP-VOE had a history of ACS in the 24 months prior to lovo-cel infusion. As of data cutoff, thirteen had no episodes of ACS following lovo-cel. One subject had one event of ACS at Month 34. This subject had achieved VOE-CR, VOE-CR24, and GR but experienced recurrent VOEs since Month 24.

Only one subject with no history of ACS in the 24 months prior to signing informed consent had ACS post lovo-cel. This subject failed VOE-CR and both parameters of GR, and has had recurrent episodes of VOE and ACS following lovo-cel infusion.

Reviewer comment: *Stroke and ACS contribute significantly to morbidity and mortality in patients with sickle cell disease. While the study was not designed to statistically evaluate the effect of lovo-cel on resolution of specific types of VOEs, most subjects with a history of these serious events prior to lovo-cel have not experienced a recurrence.*

Opioid Use

Between 6 and 12 months following lovo-cel infusion, 21/36 subjects (58.3%) reported opioid use. Between 12 and 18 months, 17/35 subjects (48.6%) reported opioid use. Per the Applicant, 48% of subjects enrolled on the LTFU study reported opioid use. The indication for opioid use is not documented, however, the Applicant states that opioids were prescribed for both sickle cell and non-sickle issues.

Reviewer Comment:

- *Because 48%-58% of subjects reported opioid use during the primary efficacy evaluation period of 6 to 18 months, some subjects who achieved VOE-CR may have masked or managed VOEs by using opioids without seeking medical care for pain.*
- *Because pain is one of the most important contributors to poor quality of life in patients with SCD, patients considering this treatment should be aware that nearly half of the subjects treated with lovo-cel reported opioid use for years after lovo-cel treatment.*
- *Similar percentage of SCD patients who undergo successful hematopoietic stem cell transplantation continue to require opioids long-term.*

Disease-Modifying Therapies

Medications

Twenty-nine subjects had history of HU usage, and six subjects had history of L-glutamine usage prior to lovo-cel. All subjects stopped HU at least 90 days and L-glutamine 7 days prior to conditioning, except one subject who inadvertently remained on L-glutamine through Day +28 when it was discontinued. No subjects were started on disease-modifying therapies after lovo-cel infusion as to do so would have interfered with the efficacy evaluation.

Reviewer comment: *Because disease-modifying drugs were not started after lovo-cel, there is no information on drug interactions between these drugs and lovo-cel.*

Transfusions

Thirty-four of the 36 subjects had a history of pRBC transfusions prior to lovo-cel, eight of whom were on chronic transfusion therapy, defined as receiving ≥8 pRBC transfusions annually in the 2 years prior to signing informed consent. Thirty-four of the 36 subjects, including all eight subjects on chronic transfusion, have received no transfusions since day +90. Most subjects were transfusion independent by Day +60. The two subjects who required transfusion beyond day +90 are:

- Subject (b) (6) . This subject was not transfusion dependent prior to lovo-cel but became transfusion dependent following lovo-cel. This subject has α-thalassemia trait and dyserythropoeisis and discussed in detail in section 6.1.12.5 of this memo.
- Subject (b) (6) . This subject received a transfusion on day +18 and then remained transfusion independent until month 35 when he experienced an SAE of obstructive pancreatitis requiring surgical intervention. He received two transfusions for supportive care and pre-operative management during the acute event. As of 60 months post lovo-cel infusion, the subject has not required additional transfusions.

Reviewer comment: *There was a notable reduction in pRBC transfusions following treatment with lovo-cel. Most subjects, including the eight with history of chronic transfusion therapy, did not require any transfusions following hematologic recovery from the myeloablative conditioning regimen.*

6.1.12 Safety Analyses

6.1.12.1 Methods

The ITT population (all subjects who initiated any study procedure beginning with stem cell collection [N=54]) was the primary population for the safety analysis.

All nine subjects in Groups A and one subjects in Group B underwent BM harvest for stem cell collection. The majority (10/11; 91%) underwent two or more harvests to collect sufficient number of cells for manufacture and rescue cells.

One subject in group B and all group C subjects (44/54) underwent plerixafor mobilization and apheresis for stem cell collection. Plerixafor dose ranges were 0.23 to 0.26 mg/kg per apheresis day. The majority (26/44; 59%) underwent two or more cycles of mobilization to obtain the sufficient number of cells for manufacture and rescue.

Myeloablative conditioning utilized busulfan as a single agent. Busulfan dosing and exposure was increased throughout the protocol amendments. Of 54 subjects, 45 initiated conditioning (7 subjects in Group A, 2 subjects in Group B, and 36 subjects in Group C). Group C subjects had a median dose of 3.4 mg/kg/day (median area under the curve: 4,842 µM/min).

Lovo-cel was administered intravenously as a single dose on Day 1. Multiple lovo-cel lots were required for some subjects to meet dose requirements (three subjects received three lovo-cel lots each).

6.1.12.2 Overview of Adverse Events

All subjects had at least one AE related to SCD, cell procurement, conditioning, or drug product. Adverse events that occurred after initiation of lovo-cel infusion were considered treatment-emergent AEs.

Subjects most commonly experienced AEs of nausea (47/54, 87.0%), thrombocytopenia (42/54, 77.8%), stomatitis (41/54, 75.9%), and sickle cell anemia with crisis (36/54, 66.7%), consistent with busulfan conditioning and underlying disease.

Adverse Events that occurred in at least 10% of subjects post infusion of lovo-cel are summarized in the table below.

Table 13: Adverse Events That Occurred in at Least 10% of Subjects Post Lovo-cel

Preferred Term	All Grades (%)	Grade 3 and 4 (%)
Abdominal pain	17	6
Alanine aminotransferase increased	11	15
Alopecia	15	0
Aspartate aminotransferase increased	15	15
Blood alkaline phosphatase increased	22	0
Constipation	44	0
Cough	15	0
Decreased appetite	13	9
Diarrhea	28	4
Dizziness	15	0
Dry skin	20	2
Epistaxis	19	4
Fatigue	24	2
Headache	17	2
Hyperglycemia	20	2
Hypoalbuminemia	11	0
Hypocalcemia	11	0
Hypokalemia	24	2
Hypomagnesemia	17	6
Hyponatremia	17	0
Insomnia	17	0
Nausea	37	13
Edema peripheral	11	0
Oropharyngeal pain	11	0
Pain in extremity	17	0
Pruritus	19	0
Pyrexia	26	7
Rash	13	0
Skin hyperpigmentation	24	0
Transaminases increased	11	0
Vision blurred	11	0
Vomiting	30	7

Source: FDA analysis based on 3-month safety update ADAE
Abbreviation: ADAE=Adverse Event Analysis.

There were two infusion-related reactions to lovo-cel that occurred in two subjects. Both reactions were Grade 1 (hot flush and decrease in diastolic blood pressure) and resolved.

Five subjects had 14 AEs assessed by the investigator as related to lovo-cel. These included an event of hot flush on the day of infusion, febrile neutropenia after busulfan conditioning, decrease in diastolic blood pressure during lovo-cel infusion, anemia, and neutropenia.

Reviewer Comment*: For the PI, FDA agreed to use Adverse Reactions above Grade 3 and above 5% following treatment (n=45) (Day 1 to Month 24), which included AEs from busulfan conditioning.*

Table 14: Adverse Reactions ≥Grade 3 (>5%) Following Treatment With LYFGENIA From Day 1 to Month 24 (N=45)*

Adverse Reaction	Grade 3 or Higher n (%)
Blood and lymphatic system disorders	-
Thrombocytopenia	31 (69)
Neutropenia	27 (60)
Febrile neutropenia	20 (44)
Anemia[a]	15 (33)
Leukopenia	15 (33)
Sickle cell anemia with crisis[b]	7 (16)
Gastrointestinal disorders	-
Stomatitis	32 (71)
Nausea	4 (9)
General disorders and administration site conditions	-
Pyrexia	3 (7)
Infections and infestations	-
Bacteremia	3 (7)
Investigations	-
Aspartate aminotransferase increased	8 (18)
Alanine aminotransferase increased	6 (13)
Gamma-glutamyl transferase increased	6 (13)
Blood bilirubin increased	3 (7)
Metabolism and nutrition disorders	-
Decreased appetite	5 (11)
Respiratory, thoracic, and mediastinal disorders	-
Pharyngeal inflammation	5 (11)

Source: Prescribing Information* Includes adverse events associated with busulfan myeloablative conditioning and underlying sickle cell disease.
a. Includes a patient with α-thalassemia trait who was diagnosed with myelodysplastic syndrome after Month 24.
b. Includes events prior to Month 6 and non-adjudicated occurrences.
Abbreviation: n (%)=number of subjects with the specified characteristic.

6.1.12.3 Deaths

There was a total of three deaths; one death occurred during the 2-year study period, and the other two deaths occurred 3 years and 5.5 years after lovo-cel infusion, respectively.

There was one death reported during the study. Subject (b) (6) experienced a fatal SAE of sudden death 616 days after receiving lovo-cel. An autopsy concluded that the cause of death was cardiovascular disease with contributing SCD and asthma. At the time of the death, FDA had an informal teleconference with the Applicant to discuss this case. FDA agreed on the causality of death.

Two additional deaths due to AML are described below.

6.1.12.4 Nonfatal Serious Adverse Events

There were 44 subjects (44/54, 81.5%) with at least 1 SAE. SAEs were generally consistent with required procedures and treatments typical of BM transplants, as well as underlying disease. Subjects most commonly experienced SAEs of sickle cell anemia with crisis (29/54, 53.7%) and pain and device related infection (5/54, 9.3% each).

There were 12 subjects who had 16 thromboembolic events. Of the 16 events, 6 events in 5 subjects were SAEs.

Reviewer comment: *Four of the 6 SAEs of thrombosis were catheter-related and occurred prior to lovo-cel infusion. One SAE of pulmonary embolism occurred after infusion.*

Two subjects had life-threatening AEs:

Subject (b) (6) (group C) was diagnosed with oral mucositis that resulted in serious epiglottitis on Day 14. Due to progressive airway compromise, the subject was transferred to pediatric intensive care, where neck X-ray showed complete airway obstruction. Treatment with dexamethasone was initiated, and the subject had an endotracheal tube placed in the operating room. On Day 15, cultures tested positive for methicillin-resistant *Staphylococcus aureus*. The subject remained intubated for 1 week while on antibiotics. The SAE of Epiglottitis resolved on Day 22 and was attributed to conditioning with busulfan.

Subject (b) (6) (group C) was treated with lovo-cel and remained hospitalized for approximately 1 month with persistent anemia and thrombocytopenia. She developed left flank and pleuritic pain and was diagnosed with an SAE of Splenic hematoma on Day 42. She required ongoing pRBC and platelet transfusions. The SAE of Splenic hematoma resolved on Day 57 and was attributed to conditioning with busulfan. The subject achieved platelet engraftment on Day 136.

6.1.12.5 Adverse Events of Special Interest

<u>Hematologic Malignancy:</u>

There were two cases of AML and one case of MDS as detailed below.

Subject (b) (6) (group A) developed blast cells, was diagnosed with MDS approximately 3 years after lovo-cel infusion, and was diagnosed with AML 5 months later. The pertinent clone did not contain an LVV integration site (IS), thus ISA was uninformative with respect to diagnosis. The AML was attributed by the investigator to busulfan conditioning, which is known to increase the risk of malignancy during HSCT and part of the treatment regimen for administration of lovo-cel. This subject died due to AML complications.

Subject (b) (6) (group A) was diagnosed with AML based on the observation of blasts in the PB and BM approximately 5.5 years after lovo-cel infusion. This subject had IS that were transiently above 10% RelFreq during linear-amplification mediated polymerase chain reaction monitoring during early follow-up that did not show clonal predominance of cells. However, an IS in the *VAMP4* gene in a pertinent clone was detected above 10% RelFreq using shearing extension primer tag selection/ligation-mediated polymerase chain reaction approximately 4

years after lovo-cel infusion, but the subject had a very low VCN. A high RelFreq in the presence of low VCN is indicative of a low clonal contribution. At Month 54, the *VAMP4* IS had a 20% RelFreq and overall VCN of 0.04 c/dg, with a clonal contribution of 1%. However, all parameters increased by the next ISA at Month 60 to approximately 60% RelFreq, with a VCN of 0.124 c/dg and a clonal contribution of 7%. The increase in VCN to 0.124 c/dg, coupled with a RelFreq >30% at the subsequent ISA, was cause for concern. Concurrent with this rise in VCN, decreases in white cell and neutrophil count were observed. Subsequent detection of blast cells led to a diagnosis of AML. This subject died after recurrence of AML.

Subject (b) (6) (group C) was 12 years of age at consent (July 18, 2019), with SCD (βS/βS genotype), chronic pain, TIA, silent stroke, and α-thalassemia trait (the presence of two *α-globin* gene deletions [-α3.7/-α3.7 genotype]). This subject was anemic and had been on pRBC transfusions at 8 years of age, with a median (min, max) total Hb of 7.6 (7.3, 7.8) g/dL (N=5) from February 2010 to February 2015 (approximately 4 years prior to enrollment). Transfusions were initiated in 2015 in response to events of TIA and silent stroke, such that the subject had a total Hb of 9.7 g/dL at baseline. Despite continued pRBC transfusions, the subject experienced eight sVOEs.

The subject remained anemic after treatment with lovo-cel, with unsupported (i.e., at least 3 months after last pRBC transfusion) total Hb values at a low value of 8.8 g/dL at Month 6, thereafter showing a gradual increase to 9.8 g/dL at Month 18. He had mild neutropenia and thrombocytopenia that resolved with B12 therapy and anemia (although better than pre-gene therapy and not transfusion dependent) and erythroid dysplasia since year 1 routine BM in 10% to 20% of erythroid precursors with persistent trisomy 8 and tetrasomy 8.

A decreased myeloid to erythroid ratio was reported (<1.0:1), indicating excess cells from the erythroid lineage compared to those from the myeloid lineage. Dysplasia was restricted to the erythroid lineage, with myeloid lineages and megakaryocytic lineages reported as normal. Notably, pre-transplant BM smears were not performed either as standard of care or per the schedule of events at the time (Protocol V 9.0, January 8, 2019). The subject also had elevated target cells in PB smears at Month 12, Month 15, and Month 18.

A Month 24 marrow showed trisomy 17. At Month 30, there was stable anemia. BM aspirate showed 15% to 20% dysplasia. Local fluorescence in situ hybridization-myelodysplastic syndrome (FISH-MDS) panel showed abnormalities on chromosomes 5, 7, 8, 13, and 17, gain of 20q, and a gain of *KMT2A*. The central and local lab results were discordant, as there were no abnormalities seen in the FISH-MDS panel from the BM, but the karyotype showed a clonal abnormality. At a tumor board discussion, the board concluded that this subject has satisfied the definition of MDS.

Reviewer comments:

Following the occurrence of MDS/AML in the two subjects treated in group A, the Hgb-206 protocol was amended to introduce screening tests for chromosomal abnormalities and genetic mutations associated with hematologic malignancies.

This included testing with conventional cytogenetics (karyotyping) and next-generation sequencing (NGS). FISH cytogenetic analysis was also conducted and was changed to a reflexive assessment in Protocol Hgb-206 V12.0 due to discordant results with other assays. As genetic testing assessments were introduced into the schedule of procedures in later versions of the study protocol, few subjects had genetic testing data available.

Both subjects in Group A were diagnosed with AML and subsequently died. This is an important safety risk to convey to patients and providers.

Excerpt from Consult in 2021 by special government employee for IND 15905/BLA 125788:

> *There is a background risk of hematopoietic malignancies in individuals with sickle cell disease. In this study (Brunson et al. 2017), the investigators used the California Cancer Registry to test whether patients with sickle cell disease are at increased risk of developing leukemia: 6,423 SCD patients were identified from 1991 to 2014, and were observed for a total of 141,752 person-years, with a median length of follow-up of 22.2 person-years. A total of 115 SCD patients were diagnosed with first primary cancers at a median age of 46 years. Among the 6,423 SCD patients, 12 (0.2%) developed leukemia; 15 (0.2%) developed lymphoma; and 4 (0.1%) developed multiple myeloma. These data are available in the paper's supplemental data. Compared to the general population in California, SCD patients had a 72% increased risk of hematopoietic malignancies. A second study (Seminog et al. 2016) has shown a similar finding: Considering all hospital admissions in England over 12 years, cancer in individuals with SCD were compared to individuals without SCD—eight cases of AML occurred, and the rate ratio for AML was 11.0, with 95% confidence interval, 3.86-30.17, which was statistically significant.*
>
> *The risk of therapy-related hematologic malignancy following allogeneic-HSCT for sickle cell disease was reported by Dr. Mary Eapen and colleagues from the Center for International Blood and Marrow Transplant Registry in 2019 (Eapen et al. 2019). They found that 6 of 910 patients developed cancer: acute myeloid leukemia [n=2], myelodysplastic syndrome [n=2],* TCR-β *gene rearrangement positive T-cell large granular lymphocytic leukemia [n=1], and one solid tumor, a hepatic myelofibroblastic tumor. Thus, the frequency of developing a therapy-related leukemia after allogeneic hematopoietic stem cell transplantation for sickle cell disease is 5/910=0.5%.*

As noted, there is a higher risk of malignancy in patients with sickle cell disease based on a few studies. Natural history studies would be optimal at knowing the true rate of hematologic malignancy in this patient population.

Based on the totality of the data from Hgb-206, the rate of malignancy is 5.5% (3/54) with lovo-cel compared to 0.5% post allogeneic HSCT who also received a myeloablative conditioning regimen.

For the Subject in group C, the Applicant stated that a diagnosis cannot be fully established. FDA has adjudicated this subject as having MDS since Month 12 following treatment; previously, this subject's findings were attributed to "stress erythropoiesis" but with the follow-up marrows with persistent cytogenetic abnormalities and persistent dysplasia, this meets criteria for MDS. We discussed this case with the Special Government Employee.

Follow-up assessment on Subject (b) (6) *includes the following:*

> *At Month 30, subject was persistently anemic, with Hb 10.1 g/dL. BM aspirate showed stable 15% to 20% dysplastic erythroid progenitors, normal megakaryocytes, and normal myeloid elements. Cytogenetic analysis was*

performed locally and centrally. Local FISH using an MDS panel on BM showed abnormalities in chromosomes 5, 7, 8, 13, and 17, gain of 20q, and gain of KMT2A*. Local karyotype showed two clones: ins(5;1)(q15;q24q42) and t(6;9)(p23;q32). Central laboratory results showed no FISH abnormalities but did show similar cytogenetic abnormalities: ins(5;1)(q22;q32q42) and one cell with t(6;9)(p21;q22). Note that the banding nomenclature differs between the local versus central labs, and one is likely correct—the labs could resolve this discrepancy by comparing the images of the banded chromosomes. However, the actual breakpoints are somewhat immaterial, as most would consider cytogenetic abnormalities sufficient for diagnosing an MDS in combination with dysplasia and anemia, as was decided by the local tumor board.*

FDA had an informal teleconference with the Applicant on December 1, 2023, to relay our position on a boxed warning for hematologic malignancy. FDA explained that the ITT population of N=54 would be used for the safety evaluation, which includes the two subjects in group A who have developed AML. We acknowledged that there is an underlying risk of baseline mutations and malignancy in patients with SCD due to ongoing hemolysis and stress on the marrow compared to that in individuals without SCD, and that changes made in the transplant and manufacturing processes can mitigate the risk of malignancy by reducing hemolysis and stress on marrow. However, one cannot say that no case of malignancy will occur because mechanisms of chemotherapy and risks following transplant (cells with driver mutations predispose to malignancy), are part of the process and carry inherent risk of malignancy regardless of type of gene therapy.

We stated that final product has always consisted of BB305-transduced CD34+ enriched autologous HPCs, and the BB305 LVV structure, design, and function were the same throughout clinical development of the product. Therefore, it is appropriate to assess the safety of lovo-cel based on the totality of the clinical experience, which includes the safety population in groups A, B, and C.

The Applicant changed their manufacturing between group A and group C to increase VCN (potentially raising unknown theoretical risk) and cell number (potentially lowering unknown theoretical risk), however the Applicant has not shown any data as to how these manufacturing changes would decrease the risk of malignancy/MDS/AML, as there is one case of MDS in group C. Moreover, not all subjects in group C have been followed post 5 years to observe a case of malignancy as was seen in group A to determine if there is truly a difference in the rate of malignancy.

Hematologic malignancy is a major safety concern from treatment that has resulted in death, and it is essential that it be considered in assessing the risks and benefits of using this product, as there is a clear potential risk of unknown magnitude with the necessity of a boxed warning.

The Applicant included a boxed Warning, and FDA accepted the language in the PI.

Oligoclonality:

Four subjects were identified with oligoclonality: Subjects (b) (6)

Subject (b) (6) had the diagnosis of AML and died due to respiratory failure. Subject (b) (6) had the diagnosis of AML and died due to recurrent AML.

The other two subjects have been reported with persistent oligoclonality. Subject (b) (6) has had bone marrow assessments yearly for 3 years. At year 3, both PB and BM ISA results had decreased for the 4 insertions sites of interest. It appears all clones are decreasing.

No bone marrow assessments have been performed to date for Subject (b) (6) .

Alpha-Thalassemia Trait:

There are two subjects with two *α-globin* gene deletions [-α3.7/-α3.7 genotype]: Subject (b) (6) and Subject (b) (6) . Subject (b) (6) has developed MDS and is described above under Hematologic Malignancy.

Subject (b) (6) (group C), SCD (βS/βS genotype), who has an α-thalassemia trait (the presence of two *α-globin* gene deletions [-α3.7/-α3.7 genotype]; about 6.5 months post lovo-cel in February 2021, PB showed white blood count 7,000/μL, Hb 7.0 g/dL, mean corpuscular volume 88, platelets 272,000/μL), with no blasts and low reticulocytes (absolute retic count of 0.35). Direct antiglobulin test was negative. A BM biopsy revealed hypoplasia of early myeloid precursors with progressive maturation, reduced cellularity with relative erythroid hypoplasia, megakaryocytes without dysplasia, Myeloid:Erythroid ratio of 1.1:1, and no abnormal blast population, but FISH showed trisomy 8 in 6% (12/200) cells; 4.5% to 9.5% of cells showed signals consistent with tetraploidy. The subject was given a tentative diagnosis of MDS. However, a repeat BM biopsy performed 1 month later did not show trisomy 8 by FISH; karyotype and single nucleotide polymorphism microarray were both normal. NGS panel showed no mutations, but *ATM* was not included in this panel. Diagnosis was changed to "transfusion-dependent anemia." Subject has persistent anemia for which she is transfused. FISH, single nucleotide polymorphism microarray, and molecular NGS panel testing were performed on the retained drug product as well as the BM-negative fraction preconditioning; all were reported to be normal. She continues to be transfusion dependent. In February 2023, an MDS panel by FISH on PB and BM showed normal results with no evidence of monosomy 5, deletion 5q, monosomy 7, deletion 7q, trisomy 8, or deletion 20q, which were previously noted on BM pathology. In March 2023, the investigator confirmed that the subject continues to receive pRBC transfusions every 2 to 3 months and maintains the argument that transfusion dependence is likely due to α-thalassemia trait and high VCN in the PB resulting in globin chain imbalance/unstable Hb.

Reviewer comment: *This subject's history post infusion is concerning for progression to MDS. Per SGEassessment:*

> *The Brigham and Women's Hospital Rapid Heme Panel consistently identified a deleterious* ATM *variant that is most likely germline, based on the recurrent nature of its identification at a high variant allele frequency. It appears that this individual was never tested for the suspected germline nature of this deleterious variant, which would confer independent risk for the development of hematopoietic malignancies.*

It remains unclear why this subject's MDS panel would change with an initial diagnosis confirmed and the cytogenetic abnormalities revert to normal. Confirmation of germline testing of this subject for the suspected germline ATM *variant should be performed. If*

confirmed, this subject has a germline predisposition to hematopoietic malignancies and for the possibility of developing MDS in this subject. It is unclear why the Applicant has not performed this testing, but this subject needs close follow up.

6.1.12.6 Clinical Test Results

Please see Section 6.1.11 for evaluation of Hb levels.

Depletion of neutrophils and platelets was observed as subsequent to myeloablative conditioning. Subjects were monitored for neutrophil and platelet engraftment while hospitalized. Successful neutrophil engraftment was defined as three consecutive absolute neutrophil count laboratory values ≥0.5×10^9 cells/L, obtained on different days after the initial post-transplant nadir by Day 43, and without receiving backup cells for rescue at any time during the neutropenic phase.

Platelet engraftment was defined as three consecutive platelet count values over 50×10^9 cells/L obtained on different days after the initial post-transplant nadir without receiving any platelet transfusions for 7 days immediately preceding and during the evaluation.

All 45 treated subjects achieved both successful neutrophil and platelet engraftment. No subjects received backup cells for rescue. The median time for neutrophil engraftment was 20 days (min; max: 12; 35). The median time for platelet engraftment was 37 days (min; max: 19; 235).

Two subjects had platelet engraftment after Day 100. One subject (Subject (b) (6)) experienced thrombocytopenia from Day 7 to Day 109 and achieved platelet engraftment on Day 134. Prior to engraftment, she received 17 platelet transfusions. The second subject (b) (6) experienced thrombocytopenia on Day 1 to 122 with events of epistaxis and a splenic hematoma on Day 42 to 57. On Day 136, she achieved platelet engraftment while receiving eltrombopag from Day 108 to Day 234. Prior to engraftment, she received a total of 67 platelet transfusions.

Reviewer comment: *It was noted that there were four subjects (three in group A and one in group C) that received granulocyte colony-stimulating factors following treatment of lovo-cel and prior to neutrophil engraftment and recovery. No other forms of cytokine support were received prior to neutrophil engraftment and recovery.*

A total of 18 subjects received steroids post lovo-cel infusion. Thirteen received hydrocortisone for prophylaxis for drug product infusion and platelet transfusions or for AEs unrelated to engraftment. Four subjects received dexamethasone, three subjects received methylprednisone, one subject received prednisone, and one subject received triamcinolone. The majority of these were given for AEs. It is unlikely that the minimal duration of steroid use had any effect on platelet engraftment and recovery.

For the two subjects who had delayed platelet engraftment:

Subject (b) (6) *also developed anemia and is now transfusion dependent (not transfusion dependent prior to this therapy) with concern for development of MDS.*

Subject (b) (6) *received eltrombopag for decreased platelet count from Day 108 to Day 234 with platelet engraftment occurring on Day 136. The day of platelet engraftment is adjudicated to the day post discontinuation of the thrombopoietin mimetic.*

No subject with delayed platelet engraftment had BM evaluations performed due to the delay in engraftment.

Abnormal chemistry values were mild transient and were not associated with AEs.

There was a general trend of decreased levels of T and B lymphocyte subsets from baseline after treatment with lovo-cel, as expected after myeloablation.

6.1.12.7 Dropouts and/or Discontinuations

There were no AEs that led to study withdrawal or discontinuation.

6.1.13 Study Summary and Conclusions

The most concerning risk associated with lovo-cel therapy is hematologic malignancy with AML/MDS. There have been three cases identified thus far. There is also a potential risk of insertional oncogenesis. The safety profile indicates delayed platelet and neutrophil engraftment, which puts patients at risk of serious bleeding events and life-threatening infections. The most commonly reported side effects included stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia, consistent with chemotherapy and underlying disease. There are also minimal risks associated with apheresis.

7. Integrated Overview of Efficacy

We did not perform an integrated overview of efficacy and did not include efficacy data from Hgb-205, Hgb-206 groups A and B, or Hgb-210 in the label for the following reasons:

- Subjects in Hgb-205 and Hgb-206 groups A and B received a drug product manufactured from BM using a different manufacturing process. There is no comparability assessment included between the product those subjects received and the commercial product approved with this BLA.
- Subjects in Hgb-210, the ongoing Phase 3 trial including subjects 2 years of age and older, received a product comparable to the commercial product. However, the difference in the age of enrolled subjects may affect the benefit-risk assessment, tolerability of study therapy, secondary malignancies, and impact of the evolving therapy on clinical manifestations and organ damage from SCD.

While we did not perform an integrated overview of efficacy, a brief summary of the data from Hgb-210 is as follows: As of February 13, 2023, 11 subjects have been treated on Hgb-210, 9 adult and 2 pediatric subjects. The pediatric subjects are 15 and 17 years of age. The two pediatric subjects have reached 24 months of follow-up. Both have achieved VOE-CR, sVOE-CR, and GR. The other nine subjects have less than 6 months of follow-up and therefore have not reached the efficacy evaluable period of 6 to 18 months.

8. INTEGRATED OVERVIEW OF SAFETY

While we did not perform an integrated overview of safety with inclusion of Study Hgb-210, a brief summary of the data from Hgb-210 is as follows: As of February 13, 2023, 16 subjects have initiated mobilization and 11 subjects have been treated. The SAEs of the ITT population are reflective of the safety profile seen in Hgb-206. All eight subjects evaluable for neutrophil engraftment have achieved it with a range of 16 to 34 days. All nine subjects evaluable for platelet engraftment have achieved it with a range of 8 to 141 days. Three subjects have had platelet recovery prior to neutrophil recovery. There have been no deaths. Neither subject with 24 months of follow-up had evidence of oligoclonality on ISA.

8.4 Safety Results

8.4.8 Adverse Events of Special Interest

After the 3 month safety report, there was an additional subject in Study Hgb-210 who had delayed platelet engraftment on Day 157. This subject received a total of 32 platelet transfusions prior to engraftment.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No animal studies of reproduction or developmental toxicity have been performed, and lovo-cel has not been studied in pregnant women.

A negative serum pregnancy test was confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and lovo-cel administration.

There are insufficient exposure data to provide a precise recommendation on duration of contraception following treatment with lovo-cel.

Women of childbearing potential and men capable of fathering a child should use an effective method of contraception (intrauterine device or combination of hormonal and barrier contraception) from start of mobilization through at least 6 months after administration of lovo-cel.

Reviewer comment: *These risks should be relayed to the patient and was included in the PI. The risk of infertility with the use of myeloablative conditioning and the options for fertility preservation should be clearly communicated with the patient.*

9.1.2 Use During Lactation

There is no information regarding the presence of lovo-cel in human milk, the effect on the breastfed infant, and the effects on milk production. This was relayed in the PI.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

This application is exempt from the Pediatric Research Equity Act because it is intended for a biologic product for which orphan designation has been granted. This product was evaluated in eight pediatric subjects.

9.1.5 Geriatric Use

Lovo-cel has not been studied in subjects over 65 years of age.

10. CONCLUSIONS

The results from the interim analysis demonstrated a clinically meaningful benefit in resolution of VOEs in 87.5%. The most commonly reported adverse reactions include stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia. Delayed platelet and neutrophil engraftment are potential risks of this therapy. Hematologic malignancy with potential of insertional oncogenesis is an inherent risk to LVV vectors in conjunction with busulfan myeloablation.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 15: Risk-Benefit Considerations and Recommendations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Sickle cell disease is a hereditary disorder of abnormal hemoglobin production resulting in vaso-occlusive events (VOEs) in which the misshapen red blood cells stick together and block blood from flowing smoothly through the blood vessels, thereby impairing oxygen delivery to organs throughout the body. • SCD primarily affects Black/African Americans with 1 in 365 Black/African American babies being born with SCD. • Acute VOEs include recurrent episodes of pain, stroke, respiratory failure, enlargement of the spleen, and priapism. • Chronic impairment of oxygen delivery and anemia causes progressive, irreversible damage to all organs in the body. • People with SCD are also at risk of having life-threatening bacterial infections due to poor splenic function.	• SCD causes significant morbidity including recurrent hospitalizations and frequent school/work absences. • People with SCD have a 20- to 30-year lower life expectancy than that of unaffected individuals.
Unmet Medical Need	• The only curative option for SCD is allogeneic transplant. However, less than 20% of patients with SCD have an available stem cell donor. Additionally allogeneic transplant is associated with significant mortality primarily from infection and graft-vs-host disease. • There are disease-modifying medications, including hydroxyurea, L-glutamine, crizanlizumab, and voxelotor. These have been shown to increase Hgb levels and some have been shown to decrease frequency and severity of VOEs but not eliminate VOEs. Additionally, they require consistent, lifelong administration for efficacy.	• Only a small minority of patients with SCD are eligible for allogeneic stem cell transplant, and transplant carries its own risk of severe morbidity and mortality. All other therapies may decrease frequency and severity but are not curative. Therefore, there is an unmet need.
Clinical Benefit	• Lovo-cel showed complete resolution of VOE between 6 and 18 months following infusion in 87.5% of subjects [CI: 71, 96.5] treated on Study Hgb-206.	• Most subjects treated on this trial had history of recurrent VOE prior to treatment with lovo-cel. The clinical benefit of resolution of VOEs was demonstrated and is clinically meaningful in this patient population.
Risk	• Hematologic malignancy is the most concerning risk in subjects treated with lovo-cel. Two subjects have been diagnosed with AML and one has been diagnosed with MDS. • The most common AEs were nausea, thrombocytopenia, stomatitis, and sickle cell anemia, with crises consistent with busulfan conditioning and underlying disease.	• The risk of hematologic malignancy is concerning and are addressed in the package insert.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Risk management plans include adequate labeling in the warnings and precautions and common adverse events in the PI.	• To address the concern for hematologic malignancy, the following risk management measures will be taken: – The PI will contain a black box warning – Patients will be given a medication guide • A PMR study will include routine screening for hematologic malignancy. • A REMS was not implemented.

Abbreviations: AE=adverse event, AML= acute myeloid leukemia, CI=confidence interval, MDS= myelodysplastic syndrome, PI=package insert, PMR=postmarketing requirement, SCD=sickle cell disease.

11.2 Risk-Benefit Summary and Assessment

SCD can cause debilitating pain crises and life-threatening organ damage with symptoms starting as early as a few months of age and continuing throughout a patient's life. Patients with SCD often require recurrent hospitalizations and absenteeism from work or school, significantly affecting their quality of life. The life expectancy of patients with SCD is 20 to 30 years less than that of the general population. The only potential curative treatment option is allogeneic HSCT, which carries with it its own risks of morbidity and mortality primarily from graft-versus-host disease and infection. Additionally, most patients with SCD lack a suitable stem cell donor, and therefore transplant is not an option.

The benefits of lovo-cel include:

- It is an autologous product, which eliminates the need to find an adequate donor, does not carry the risk of graft-versus-host disease, and does not require immunosuppressive medications following infusion.
- Of subjects who had history of recurrent VOEs prior to treatment, 87.5% experienced no VOEs in the 18 months following infusion, which represents a substantial clinical benefit.

The risks of lovo-cel include:

- The most concerning risk associated with lovo-cel therapy is hematologic malignancy with AML/MDS. There have been three cases identified thus far. There is also a potential risk of insertional oncogenesis.
- The safety profile indicates delayed platelet and neutrophil engraftment, which puts patients at risk of serious bleeding events and life-threatening infections.
- The most commonly reported side effects include stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia consistent with chemotherapy and underlying disease. There are also minimal risks associated with apheresis, the process of collecting the patient's stem cells.

The overall benefit-risk profile favors approval of lovo-cel for the treatment of SCD.

11.3 Discussion of Regulatory Options

The available data supports traditional approval for the treatment of patients 12 years of age or older with SCD and a history of VOEs.

11.4 Recommendations on Regulatory Actions

There are no approved gene therapy products for SCD. There is only one currently approved product for SCD that is indicated to reduce frequency of VOEs. The efficacy of lovo-cel was VOE-CR rather than reduction in frequency of VOEs, which is a more clinically meaningful endpoint. Hence, priority review was granted for this application.

The Applicant has provided substantial evidence of effectiveness and safety based on a single well-controlled clinical investigation providing evidence of clinical benefit, supported by preclinical studies. There are major risks with infusion of lovo-cel, including hematologic malignancy, which is described in the label. However, the benefit-risk assessment is still favorable with the high degree of efficacy, and the clinical review team recommends regular

approval of lovo-cel for autologous hematopoietic stem-cell-based gene therapy for the treatment of patients 12 years of age and older with SCD and a history of VOEs.

11.5 Labeling Review and Recommendations

The revised PI was reviewed, commented on, and revised by the appropriate discipline reviewers. FDA's Advertising and Promotional Labeling Branch conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

The label has been modified to reflect the efficacy and safety data presented in this memo. The major changes to the draft label pertaining to efficacy and safety include:

1) Addition of a black box warning to include hematologic malignancy
2) Updated safety to include the subject who developed MDS
3) Updated efficacy data with the most recent data cutoff with major revisions to section 14
4) Section 2 updated to include apheresis and myeloablation dosing instead of in section 14
5) Removal of patient-reported outcome data due to a single-arm study design
6) Removal of data from subjects treated on ongoing study Hgb-210

11.6 Recommendations on Postmarketing Actions

The Applicant will conduct a postmarketing requirement safety study. With the identified risk of hematologic malignancy and potential risk of insertional oncogenesis, the previously considered registry-based analysis of spontaneous postmarketing AEs reported under section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) will not suffice. The pharmacovigilance system under section 505(k)(3) of the FDCA is also considered insufficient to assess this serious risk.

Therefore, the Applicant will be required to conduct a postmarketing, prospective, multicenter, observational study to assess the long-term safety of lovo-cel and the risk of secondary malignancies post lovo-cel administration. This postmarketing requirement study under Section 505(o) of FDCA will enroll at least 250 subjects to be followed for 15 years after product administration. The study design will specify regular monitoring for clonal expansion with adequate testing methods.