Summary Basis for Regulatory Action

Date:	December 08, 2023
From:	Graeme Price, PhD, Chair of Review Committee, Office of Therapeutics Products (OTP), Office of Gene Therapy (OGT), Division of Gene Therapy 2 (DGT2)
BLA STN:	BLA 125788/0
Applicant:	bluebird bio, Inc
Submission Receipt Date:	April 21, 2023
PDUFA Action Due Date:	December 20, 2023
Proper Name:	lovotibeglogene autotemcel
Proprietary Name:	LYFGENIA
Indication:	Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs).

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Therapeutic Products

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Graeme Price, PhD, CBER/OTP/OGT Takele Argaw, DVM, MSc, CBER/OTP/OGT Alan Baer, PhD, CBER/OTP/OGT Brian Stultz, MS, CBER/OTP/OGT Andrew Timmons, PhD, CBER/OTP/OGT Maureen DeMar, BSN, RN, CBER/OCBQ/DMPQ Zainab Mansaray-Storms, PhD, CBER/OCBQ/DMPQ Ritu Agarwal, PhD, CBER/OCBQ/DBSQC Kenneth Phillips, PhD, CBER/OCBQ/DBSQC Claire Wernly, PhD, CBER/OCBQ/DBSQC Esmeralda Alvarado Facundo, PhD, CBER/OCBQ/DBSQC Marie Anderson, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Ashley Munchel, MD, CBER/OTP/OCE Megha Kaushal, MD, CBER/OTP/OCE Deborah Thompson, MD, MSPH Peter Lenahan, DC, PhD, MPH, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Zhong Gao, PhD, CBER/OBPV/DB Harry Houghton, MS, CBER/OBPV/DB Tianjiao Dai, PhD, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Melek Sunay, PhD, CBER/OTP/OPT
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTP/OCE
Labeling • Promotional (OCBQ/APLB)	Benjamin Cyge, CBER/OCBQ/DCM/APLB Oluchi Elekwachi, CBER/OCBQ/DCM/APLB
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Lucy Godley, MD, PhD, Special Government Employee
Advisory Committee Summary	N/A

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1. Introduction

Bluebird bio, Inc submitted a Biologics License Application (BLA), STN 125788/0, for licensure of lovotibeglogene autotemcel (lovo-cel) with the proprietary name LYFGENIA. LYFGENIA is indicated for the treatment of patients 12 years of age or older with sickle cell disease (SCD) and a history of vaso-occlusive events (VOEs).

LYFGENIA 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. LYFGENIA is supplied frozen in 20 mL (b) (4) bags as a suspension for intravenous infusion after thawing. Each bag contains 20 mL of a suspension of 1.7 – 20×10^6 cells/mL. The minimum dose is 3.0×10^6 CD34+ cells/kg of patient weight.

Patients undergo HSC mobilization with plerixafor, followed by apheresis to collect the cells. The apheresis material is shipped to the manufacturing site, where CD34+ cells are selected and transduced with the BB305 LVV to manufacture LYFGENIA. Following myeloablative chemotherapy and LYFGENIA infusion, the transduced HSCs engraft into bone marrow and differentiate to reconstitute the hematopoietic system, including production of erythrocytes containing HbA^{T87Q} to treat the patient's SCD and prevent VOEs.

This document summarizes the basis for approval of LYFGENIA. Data from 54 subjects from one adequate and well controlled Phase 3 study (HGB-206) provide the primary evidence of safety and efficacy for this BLA. The recommendation for approval is based on demonstration of complete resolution of VOEs (VOE-CR) between 6-18 months in patients 12 years of age and older with sickle cell disease and a history of vaso-occlusive events. The major risks of treatment with LYFGENIA include hematologic malignancy and insertional oncogenesis.

The Applicant has provided substantial evidence of effectiveness based on an adequate and well controlled clinical trial supported by preclinical studies and PK studies. The review team recommends approval of this BLA with a safety post-marketing requirement (PMR) for a prospective, multi-center, observational study, to assess and characterize the risk of malignancies after treatment with LYFGENIA and to assess the long-term safety of LYFGENIA, and a PMR for a study to evaluate leachables of the (b) (4) bag over the duration of the shelf-life of LYFGENIA to include a full toxicological risk assessment for the identified leachables and extractables. In addition, the applicant agreed to a post-marketing commitment (PMC) related to product quality assessment.

2. Background

Sickle Cell Disease (SCD) is a hereditary blood disorder caused by a point mutation in the hemoglobin β globin gene, within codon 6 of the 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 including the lungs as acute chest syndrome (ACS), in the brain as vasculopathy and stroke, splenic or hepatic sequestrations, VOE-induced priapism associated with erectile dysfunction, but most often occur in the bones causing pain crises, the hallmark complication of SCD. VOEs are associated with both an increased risk of sudden death and cumulative disease progression. Current available therapies include pRBC transfusions, including chronic exchange transfusion, hydroxyurea (HU), L-glutamine, crizanlizumab, voxelotor, and allogeneic hematopoietic stem cell transplantation (allo-HSCT). Overall, treatment of patients with SCD remains an unmet medical need.

LYFGENIA is a biological product containing genetically modified autologous hematopoietic stem and progenitor cells (HSCs) transduced with the BB305 lentiviral

vector (LVV) encoding human $\beta^{A\text{-}T87Q}$-globin. Progeny erythrocytes derived from a modified HSC incorporate the $\beta^{A\text{-}T87Q}$-globin into adult hemoglobin (HbA) to form HbA^{T87Q}, which inhibits polymerization of sickle Hb under hypoxic conditions and leads to reduced erythrocyte sickling, preventing VOEs.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	August 30, 2013
2. IND submission	March 14, 2014
3. Fast Track designation granted	May 08, 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. Pre-BLA meeting	February 13, 2023
8. BLA 125788/0 submission	April 21, 2023
9. BLA filed	June 20, 2023
10. Mid-Cycle communication	August 15, 2023
11. Late-Cycle meeting	October 06, 2023
12. Action Due Date	December 20, 2023

3. Chemistry Manufacturing and Controls (CMC)

This BLA provides an adequate description of the manufacturing process and characterization of lovotibeglogene autotemcel (lovo-cel; LYFGENIA). The CMC review team concludes that the manufacturing process, along with associated test methods and control measures, are capable of producing a product with consistent quality characteristics.

a. Product Quality

To manufacture LYFGENIA, autologous hematopoietic progenitor cells obtained by apheresis (HPC-A) are collected from SCD patients following mobilization with plerixafor. HPC-A is collected at a Qualified Treatment Center (QTC) and shipped to the drug substance (DS)/drug product (DP) manufacturing facility (b) (4) . Here, CD34+ cells are washed (b) (4) transduced by addition of the BB305 LVV in the presence of the (b) (4) The bags containing DP are cryopreserved in a controlled rate freezer and stored in vapor phase liquid nitrogen (≤ -140°C) until thawed for use. The total manufacturing process occurs (b) (4)

The BB305 LVV is (b) (4)

Manufacturing Control Strategy

Manufacturing process consistency is assured by qualification and tracking of raw materials, critical components, and reagents, in-process monitoring and testing, manufacturing process validation and continuous process verification, and lot release and stability testing programs. Autologous product traceability is assured using a validated chain-of-identity system. Critical process parameters and critical quality attributes of LYFGENIA were defined through process characterization and validation studies. Methods used to determine product quality were validated. Manufacturing and testing comply with Current Good Manufacturing Practices. The shelf-life for BB305 LVV (b) (4)
The shelf-life for LYFGENIA stored in vapor phase liquid nitrogen (≤ -140°C) is 12 months.

Comparability Assessments

During BLA review, comparability of products manufactured at different facilities was assessed to enable pooling of clinical data. The applicant evaluated products manufactured using the clinical process at the (b) (4) (reference) site and the commercial process at the (b) (4) site. While there were differences in vector copy number (VCN) between products manufactured at the two sites, the totality of data submitted supports that the changes implemented to the DP manufacturing process do not materially impact the safety or efficacy of the lovotibeglogene autotemcel DP. As a result, the clinical data obtained from these subsets of lovotibeglogene autotemcel lots may be consolidated into a unified dataset for the clinical interpretations of safety and efficacy.

Comparability of the BB305 LVV generated by previous manufacturing processes (b) (4) and the current manufacturing process (b) (4) was also assessed. While BB305 LVV manufactured by these different processes was not comparable in certain aspects (b) (4), these differences are controlled during DP manufacture and the BB305 LVVs function similarly to generate lovotibeglogene autotemcel lots with highly similar composition and properties. Thus, vectors are sufficiently comparable to allow pooling of clinical data from lovotibeglogene autotemcel DP lots manufactured with BB305 produced in (b) (4) .

PMRs/PMCs

The following issues were identified but could not be resolved during the review cycle. These issues will be resolved through PMR/PMC by March 30, 2025.

A potential concern regarding leachables was identified with the final product container (b) (4) bag), which is not an approved or cleared cryopreservation bag (see 3.e., below). To resolve this issue, bluebird bio, Inc. will conduct a leachable compound evaluation for the (b) (4) bag over the duration of the shelf-life for LYFGENIA and a toxicological risk assessment for any identified leachable and extractable compounds as a PMR. The final study report will be submitted to FDA by March 30, 2025.

The DP in (b) (4) assay was not adequately validated for robustness. bluebird bio, Inc., will perform additional robustness assessments of this assay as a PMC. Final study reports will be submitted to FDA by December 31, 2024

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the lovotibeglogene autotemcel drug product were found to be adequate for their intended use.

LYFGENIA specifications are shown in Table 2 below:

Table 2. Final Commercial LYFGENIA Release Specifications

Quality Attribute	Test	Method	Acceptance Criteria
Potency and Strength	Vector Copy Number (VCN)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
			(b) (4)
	$\beta^{A\text{-}T87Q}$-globin Quantitative Protein Expression	(b) (4)	(b) (4) $\beta^{A\text{-}T87Q}$-globin (relative to (b) (4)
Identity	$\beta^{A\text{-}T87Q}$-globin quantitative protein expression	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
Purity and Content	(b) (4)	(b) (4)	(b) (4)

	(b) (4)	(b) (4)	(b) (4)
	Total cell concentration	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
Safety	Sterility	(b) (4)	No growth
	Endotoxin	(b) (4)	(b) (4)
	Mycoplasma	(b) (4)	None detected
Quality	Appearance	Visual assessment	Colorless to white to red, including shades of white or pink, light yellow, and orange

c. CBER Lot Release

CBER Lot Release testing, including the submission of product samples to CBER, is not required. The basis for this decision is that lovotibeglogene autotemcel is an autologous product; as such, each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of lovotibeglogene autotemcel (LYFGENIA) are listed in Table 3 below. The activities performed and inspectional histories are noted in the table.

Table 3. Manufacturing Facilities Table for lovotibeglogene autotemcel (LYFGENIA)

Name/Address	FEI number	DUNS number	Inspection /Waiver	Justification /Results
(b) (4) Drug substance manufacturing, drug product manufacturing, labeling, packaging, release testing	(b) (4)	(b) (4)	PLI	CBER/DMPQ (b) (4) VAI
(b) (4)	(b) (4)	(b) (4)	PLI	CBER/DMPQ (b) (4)

Name/Address	FEI number	DUNS number	Inspection /Waiver	Justification /Results
(b) (4) BB305 LVV intermediate manufacturing				NAI
(b) (4) Drug product release testing	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI
(b) (4) Drug product release testing	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI
(b) (4) Drug product release testing	(b) (4)	(b) (4)	Waiver	ORA/OPQO (b) (4) NAI
(b) (4) Drug product release testing	(b) (4)	(b) (4)	Waiver	ORA/OPQO MRA Inspection Review of (b)(3),(b)(4) VAI

(b) (4) CBER: Center for Biologics Evaluation and Research, DMPQ: Division of Manufacturing and Product Quality; MRA: Mutual Recognition Agreement; NAI: No Action Indicated; ORA: Office of Regulatory Affairs; OBPO: Office of Biological Products Operations; OPQO: Office of Pharmaceutical Quality Operations; PLI: Pre-license inspection; VAI: Voluntary Action Indicated.

CBER/DMPQ conducted a PLI at (b) (4) and a Form FDA 483 was issued at the end of the inspection. The firm adequately responded to the observation. All inspectional issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

CBER/DMPQ conducted a PLI at (b) (4) for the BB305 lentiviral vector manufacturing and fill/finish activities. No objectionable issues were identified, and the inspection was classified as no action indicated (NAI).

ORA/OPQO conducted a surveillance inspection at (b) (4), and the inspection was classified as NAI. The firm has experience in performing sterility and bacterial endotoxin testing.

ORA/OBPO conducted a surveillance inspection at (b) (4), and the inspection was classified as NAI. The firm is experienced in performing microbiology and mycoplasma testing.

ORA/OPQO conducted a PAI at (b) (4), and the inspection was classified as NAI. The firm is experienced in performing laboratory tests for drug components, sterile and non-sterile drug products.

(b)(3), (b)(4) conducted a surveillance inspection at (b) (4) and a GMP certificate was issued to the firm at the completion of the inspection. ORA/OPQO reviewed the inspection outcome through the MRA with (b)(3),(b)(4). OPQO concluded the inspection is consistent with a VAI classification.

e. Container/Closure System

The container closure system for LYFGENIA consists of a primary package container (a sterile, single use (b) (4) bag manufactured by (b) (4), a secondary package container (a sterile (b) (4) bag manufactured by (b) (4), and a tertiary metal package container (cryocassette). LYFGENIA DP is filled into (b) (4) bag(s) (1 bag for 20 mL DP, 2 bags for 40 mL DP) and the product transfer tubing and sample tubing are heat sealed by sterile welding. After visual inspection, the product label is applied to the bag, and it is placed inside the (b) (4) bag. The (b) (4) bags are heat sealed and inserted into a metal cryocassette labeled with patient and product information. Container closure integrity testing employing the (b) (4) method was performed by bluebird bio, Inc.; all acceptance criteria were met.

Information regarding leachable compounds testing for the (b) (4) bag over the shelf-life of the product was missing from the BLA and resulted in a PMR.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. This request and the provided supporting information was sufficient to conclude that LYFGENIA and its manufacturing process pose a negligible risk to the environment or the general public. Data provided in the BLA submission indicates that the potential for recombination of the BB305 LVV into a replication-competent form is low, and that manufacture of the vector is well controlled and poses a minimal risk of release to the environment. The potential for persistence of LYFGENIA in the environment is negligible as these cells have stringent nutritional requirements for survival and are therefore not viable in the environment. FDA concluded

that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. 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 (POC) studies in immunodeficient mice administered BB305 LVV-transduced CD34+ HSCs obtained from healthy donors displayed BM engraftment and $\beta^{A\text{-}T87Q}$-globin expression. *In vivo* POC studies were also conducted using transgenic mouse models of SCD, where murine bone marrow cells (mBMCs) were transduced with the $\beta^{A\text{-}T87Q}$ (b) (4) 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.

In vivo studies were also conducted to assess the activity and safety of mBMCs transduced with BB305 following primary and secondary transplantation in β-thalassemic and wild-type C57BL/6 mice. Long-term bone marrow engraftment and chimerism were observed in all animals receiving 11×10^6 cells/kg BB305 LVV-transduced mBMCs compared to those that received mock-transduced mBMCs at 4 months post-transplantation. In the secondary transplantation study, no deaths or adverse findings attributed to the BB305 LVV-transduced cells occurred through 6 months post-transplantation of 6×10^6 cells/mouse. The observed incidence of T-cell lymphoma and/or leukemia was within the reported range (15.7-25.3%) for radiation-associated lymphoma in C57BL/6 mice (E. Will *et a*l. (2007) Mol Ther 15:782-91) and was considered incidental.

The risk of insertional mutagenesis of BB305 LVV as evaluated using an (b) (4) assay performed with BB305 LVV-transduced mBMCs showed low mutagenic potential of BB305 LVV compared to positive control vectors (b) (4), which are known to cause insertional transformation. Integration site analysis of CD34+ HSCs obtained from healthy donors showed no enrichment for LVV integration in or near known oncogenes. Additionally, no preferred integration near or within genes that are clinically associated with either clonal dominance or with leukemia for GRV was observed.

Carcinogenicity and developmental and reproductive toxicity studies were not conducted with LYFGENIA™. These studies are not warranted based on the product characteristics and safety profile.

5. Clinical Pharmacology

The clinical pharmacology review team's recommendation for approval of LYFGENIA is based on review of data from the one ongoing Phase 1/2 study (Study HGB-206), with supportive data from one ongoing Phase 3 study (Study HGB-210), one long-term follow-up study (Study HGB-307), one Phase 1/2 study (Study HGB-205), and a population pharmacodynamic (PD) study. LYFGENIA from different manufacturing processes were used in the clinical development. Clinical pharmacology evaluation (except for dosing characteristics- and pharmacodynamic markers-related correlative analysis) focuses on

LYFGENIA from the process proposed for commercial manufacturing – DP2a (Study HGB-206 Group C).

- Subjects in Study 206 Group C (N=36) received a median (min, max) dose of LYFGENIA of 6.4(3.0, 14.0)×10^6 CD34+ cells/kg.
- After infusion of LYFGENIA, 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 cut-off date for all studies, although high inter-subject variability of PB VCN kinetic profiles were observed.
- HbA^{T87Q} generally increased steadily after administration of LYFGENIA, 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 non-transfused Hb at Month 24. Expression of HbA^{T87Q} 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 hematopoietic stem cells (HSCs).
- At Month 6 post-infusion of LYFGENIA, the median (min, max) non-transfused total Hb levels were 11.4 (5.1, 14.4) g/dL (N=33). Non-transfused total Hb levels remained durable at Month 24 with median (min, max) levels of 11.8 (6.6, 16.2) g/dL (N=34).
- The kinetic profile of HbS was similar to HbA^{T87Q}. HbS levels increased initially after administration of LYFGENIA, 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. At Month 24, the median (min, max) HbS was 5.8 (1.9, 8.0) g/dL (N=34).
- The amount of each hemoglobin (Hb) fraction as well as the total Hb was generally stable by 6 months post-infusion of LYFGENIA. The relative percentages of HbA^{T87Q} and HbS were also stable over time.
- LYFGENIA manufactured from suspension culture (sLVV) and adherent culture (aLVV) had similar median values for DP VCN and DP %LVV+ Cells. Subjects who received sLVV had higher median PB VCN levels compared to subjects received aLVV. Similar median HbA^{T87Q} levels and key efficacy endpoint (complete resolution of vaso-occlusive event, VOE-CR) were observed between sLVV and aLVV subgroups.
- The targeted AUC range of busulfan evaluated in clinical studies were considered adequate for myeloablation.
- Non-transfused total Hb at Month 6 and VOE-CR: in the evaluable subjects, 4 of 14 (29%) subjects with lower than median level of non-transfused total Hb (11.4 g/dL) did not achieve VOE-CR. All 15 subjects with greater than or equal to median level of non- transfused total Hb achieved VOE-CR.
- HbA^{T87Q} at Month 6 and VOE-CR: in the evaluable subjects: 3 of 14 (21%) subjects with lower than median level of HbA^{T87Q} (5.2 g/dL) did not achieve VOE-CR. One subject with greater than median level of HbA^{T87Q} did not achieve VOE-CR.

6. Clinical/Statistical

The clinical review team's recommendation for approval of LYFGENIA for the treatment of patients 12 years of age or older with sickle disease and a history of vaso-occlusive events is based on Study Hgb 206.

a. Clinical Program

Data in support of LYFGENIA is from Study Hgb 206, an ongoing Phase 1/2, open label, multicenter study evaluating the safety and efficacy of LYFGENIA in subjects 12 to 50 years of age with SCD.

Subjects were assigned to a group (A, B or C) based on the stem cell source and the manufacturing process. All subjects on Hgb-206 (groups A, B and C) are included in the safety evaluation (n=54). The efficacy evaluation is limited to subjects in group C who received plerixafor mobilized peripheral blood stem cells using manufacturing process 2a which reflects the commercial product. Thirty-two 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 (TP-VOE). The primary efficacy endpoint was complete resolution of VOEs (VOE-CR) between 6-18 months following LYFGENIA. Of the 32 subjects, 28 (88%; 2-sided CI: 71%, 96.5%) achieved VOE-CR. Four patients who achieved VOE-CR experienced VOEs after the primary evaluation period.

The basis of FDA's conclusion of substantial evidence of effectiveness is based on this adequate and well controlled clinical trial, supported by the clinical investigation of PK and preclinical studies, with clinically meaningful benefit as evidenced by complete resolution of VOEs in 88% of the population during the evaluable period.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were performed at three domestic clinical investigator study sites that participated in the conduct of Protocol HGB-206. The inspections did not reveal substantive issues that impact the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

This application is exempt from Pediatric Research Equity Act (PREA) because it is intended for a biologic product for which Orphan Designation has been granted. The results of the ongoing Study Hgb 206 provides evidence of clinical benefit in the pediatric population above 12 years of age.

d. Other Special Populations

The efficacy of LYFGENIA has not been studied in any other special populations.

7. Safety and Pharmacovigilance

The safety of LYFGENIA was evaluated in 54 subjects. All subjects on Hgb-206 (groups A, B and C) who received LYFGENIA are included in the safety evaluation. All subjects received busulfan myeloablative conditioning prior to receiving LYFGENIA. All subjects achieved neutrophil engraftment. Two subjects had delayed platelet engraftment post Day 100.

There were three deaths. One subject had a sudden death from an acute cardiac event at month 20 following LYFGENIA. Two subjects in Group A developed acute myeloid leukemia (AML) and subsequently died.

In addition to the two subjects who developed AML, one subject in Group C developed myelodysplastic syndrome (MDS). All three hematologic malignancies are likely related to this therapy.

The most frequent (>20%) ≥Grade 3 adverse reactions were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.

The potential risk of LYFGENIA include hematologic malignancy and insertional oncogenesis. The risk of hematologic malignancy is conveyed as a boxed warning in the label.

Pharmacovigilance Plan (PVP)

The PVP includes the sponsor's assessment of important identified and potential risks and missing information based on data collected from the nonclinical and clinical development program for lovotibeglogene autotemcel in the treatment of SCD, including safety concerns associated with gene therapy. The sponsor will conduct routine pharmacovigilance in accordance with 21 CFR 600.80 and enhanced pharmacovigilance for malignancies. Enhanced pharmacovigilance will include expedited (15-day) reporting of malignancies (regardless of seriousness or label status), including hematologic malignancies, following licensure. The sponsor will also provide a safety assessment of malignancies in periodic safety reports.

In addition to routine and enhanced pharmacovigilance, the postmarketing safety monitoring of lovotibeglogene autotemcel will include a 15-year long term follow-up (LTFU) observational safety study (REG-503), as a postmarketing requirement (PMR) under 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA), to assess the known serious risk of malignancies following administration of lovotibeglogene autotemcel. This study will enroll 250 SCD patients.

Additionally, the sponsor will conduct LTFU of clinical trial participants in the ongoing study LTF-307. The above LTFU studies are in alignment with FDA Guidance Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products.

Protocol REG-503 design and data analysis plan will be finalized with the sponsor post-licensure. Of note, an algorithm for monitoring for insertional oncogenesis, including a schedule for conducting insertion site analysis (ISA), will be agreed upon. FDA has provided recommendations on the REG-503 study methods for the PMR, including the need for additional testing for safety outcome assessment and monitoring at pre-specified intervals. Testing will include bone marrow biopsy, peripheral blood sample analyses with blood smear, ISA, vector copy number, and gene expression studies. FDA will review the final study protocol upon submission to ensure that FDA recommendations on study methods were appropriately incorporated.

8. Labeling

The proposed proprietary name, LYFGENIA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on July 13, 2023, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on July 18, 2023.

The Advertising and Promotional Labeling Branch (APLB) reviewed and provided comments on the proposed Prescribing Information, Patient Package Insert, and package and container labels on November 13, 2023.

9. Advisory Committee Meeting

This BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee because the information submitted, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

LYFGENIA has received Orphan Drug, Fast Track, and Regenerative Medicine Advanced Therapy Designations. This submission was granted priority review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness and safety based on an adequate and well controlled clinical trial, supported by pharmocodynamic and preclinical studies. The Applicant has provided evidence of a clinically meaningful benefit in complete resolution of VOEs in 88% of the efficacy evaluable population.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends approval for patients 12 years of age or older with sickle cell disease and a history of VOEs.

b. Benefit/Risk Assessment

LYFGENIA has demonstrated a clinically meaningful benefit in complete resolution of VOEs in 88% of the efficacy evaluable population.
The most commonly reported adverse reactions included stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia. The risks of LYFGENIA include hematologic malignancy and insertional oncogenesis.

The overall benefit risk profile favors approval, as there is substantial clinical benefit with complete resolution of VOEs.

The review team determined that LYFGENIA does not require a REMS. However, a PMR safety study will be required to assess the long-term risk of hematologic malignancies.

c. Recommendation for Postmarketing Activities

The sponsor will conduct routine and enhanced pharmacovigilance activities as outlined in the Pharmacovigilance Plan, and the following safety study as a PMR under section 505(o) of the FDCA, to assess the known serious risk of malignancies:

1. A postmarketing, prospective, multi-center, observational study, to assess and characterize the risk of malignancies after treatment with lovotibeglogene autotemcel and to assess the long-term safety of lovotibeglogene autotemcel (Study REG-503). The study will include 250 patients with sickle cell disease who received lovotibeglogene autotemcel, and each enrolled patient will be followed for 15 years after product administration. The study design will include monitoring (at pre-specified intervals) for clonal expansion with adequate testing strategies.

   The sponsor's proposed study milestone dates are as follows:

   Final protocol submission: March 29, 2024

   Study completion: December 31, 2043

   Final study report submission: December 31, 2044

The Applicant agreed to the following CMC PMR:

2. A study to evaluate leachables of the (b) (4) bag over the duration of the shelf-life of lovotibeglogene autotemcel. This evaluation will also include a full toxicological risk assessment for the identified leachables and extractables.

   The Applicant's proposed study milestone dates are as follows:

   Final Protocol Submission: January 26, 2024

   Study Completion Date: January 30, 2025

   Final Report Submission: March 30, 2025

The Applicant agreed to the following CMC postmarketing commitment (PMC):

3. To perform additional robustness assessments of the (b) (4) assay.
   Final Report Submission: December 31, 2024