

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125788/0

lovotibeglogene autotemcel (Lyfgenia)

**Zainab Mansaray-Storms
CMC/Facility Reviewer
DMPQ/MRBII**

1. **BLA#:** STN 125788/0

2. **APPLICANT NAME AND LICENSE NUMBER**

bluebird bio, Inc., US License #2160

3. **PRODUCT NAME/PRODUCT TYPE**

USAN: lovotibeglogene autotemcel, lovo-cel

Proprietary Name: Lyfgenia

Other names: lovo-cel; bb1111; LentiGlobin BB305 Drug Product for Sickle Cell Disease

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

a. **Pharmacological category** : Gene Therapy

b. **Dosage form**: Suspension for intravenous infusion

c. **Strength**: 1.7 to 20 x 10⁶ cells/mL

d. **Route of administration**: Intravenous infusion

e. **Indication(s)**: Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs).

5. **MAJOR MILESTONES**

Submission Received: April 21, 2023

First Committee Meeting: May 12, 2023

Filing Meeting: Jun 05, 2023

Internal Mid-Cycle Meeting: August 01, 2023

Internal Late Cycle Meeting: September 18, 2023

Pre-License Inspection (b) (4)

Pre-License Inspection (b) (4)

Action Due Date: December 20, 2023

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Zainab Mansaray-Storms, OCBQ/DMPQ/MRB1	Drug Substance, Drug Product, Facilities and Equipment

7. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
April 21, 2023	STN 125788/0	
May 30, 2023	Amendment STN 125788/0/1 (response to DMPQ IR #1 dated 23 May 2023)	DP release testing site responsibilities
October 27, 2023	Amendment STN 125788/0/19	(b) (4) response to Form 483

8. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF BB-MF (b) (4)	(b) (4)	(b) (4) (stopper)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to facility is provided in the BLA and/or reviewed during pre-license inspection of (b) (4)

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

bluebird bio, Inc. (bluebird) submits BLA125788/0, for a new gene therapy product lovotibeglogene autotemcel (lovo-cel) for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso occlusive events (VOEs). lovo-cel consists of autologous CD34+ cells containing hematopoietic stem cells (HSC) which are transduced with a BB305 lentiviral vector (LVV) encoding β^{A-T87Q} -globin.

The drug substance (DS) critical component (i.e., BB305 LVV) is manufactured at the (b) (4) site, (abbreviated as (b) (4)) and lovo-cel DS and drug product (DP) are manufactured at the (b) (4) site (abbreviated as (b) (4))

DMPQ conducted a pre-license inspection (PLI) at (b) (4) in (b) (4) and a one item 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).

DMPQ performed a PLI at the (b) (4) facility in (b) (4) for the BB305 LVV manufacturing and fill/finish activities. No Form 483 was issued at the end of this PLI, and the inspection was classified as No Action Indicated (NAI).

This review memo covers areas including Chemistry and Manufacturing Controls (CMC) with focus on microbial controls, and facilities with focus on facility and major equipment qualification, cleaning, environmental monitoring (EM), utilities and controls of cross-contamination.

Based on review of this BLA submission and amendment which addressed DMPQ information request, and the outcome of the manufacturing facility inspections, approval of this BLA is recommended.

B. RECOMMENDATION

I. APPROVAL

Based on information reviewed in this submission and the outcome of the manufacturing facility inspections, approval is recommended.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Zainab Mansaray-Storms Consumer Safety Officer OCBQ/DMPQ/MRBII	Concur	
Anthony Lorenzo Branch Chief OCBQ/DMPQ/MRBII	Concur	
Carolyn Renshaw Division Director OCBQ/DMPQ	Concur	

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Module 3

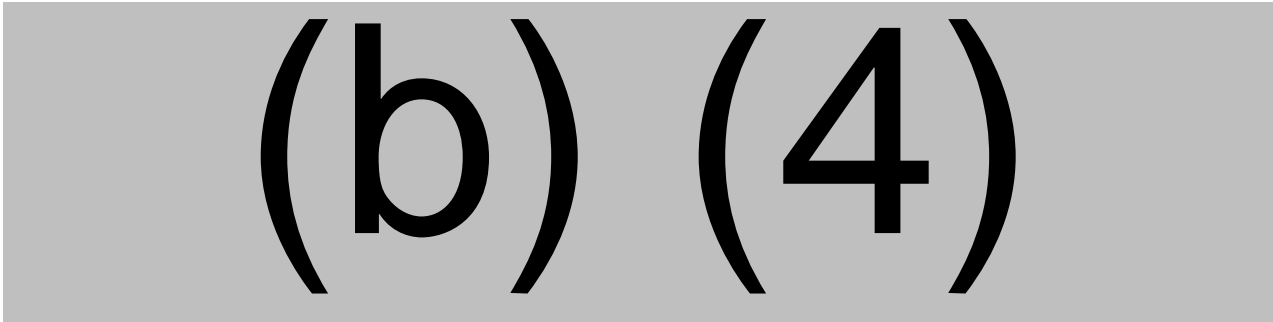
lovo-cel DS is an autologous CD34+ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced with BB305 LVV encoding the β A-T87Q-globin gene. The manufacturing of the BB305 LVV and lovo-cel DS are submitted as separate 3.2.S *Drug Substance* and it is as such reviewed separately.

3.2.S DRUG SUBSTANCE (BB305 Lentiviral Virus)


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3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The lovo-cel drug product consists of an autologous CD34+ cell-enriched population obtained from patients with Sickle Cell Disease that contains hematopoietic stem cells transduced with BB305 lentiviral vector encoding the β A-T87Q-globin gene, suspended in (b) (4) cryopreservation solution containing 5% dimethylsulfoxide. The β A-T87Q-globin gene encodes the human, adult, β A-globin with a glutamine amino acid residue substituted for a threonine at position 87.

lovo-cel is administered as a single dose by intravenous infusion. A single lot of drug product may consist of one or two bags.

3.2.P.2.5 Microbiological Attributes

Microbiological attributes are provided in Section 3.2.P.7 *Container Closure System* of this review memo.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

Facility	FEI/DUNS Numbers	Responsibility
(b) (4)	(b) (4)	Drug product manufacturing, labeling, packaging, in-process and release testing, drug product storage

3.2.P.3.3 Description of Manufacturing Process

Manufacture of lovo-cel DP continues from the manufacture of lovo-cel DS (b) (4). The DP manufacturing process consists of the Formulation and Cryopreservation step, which includes (b) (4) of transduced CD34+ cells in the cryopreservation solution, filling into one or two cryopreservation bags, and freezing.

(b) (4)

Depending on the total cells available for cryopreservation, the volume of cryopreservation solution is selected to accommodate necessary sampling and yield, either 20 mL (1 bag) or 40 mL (2 bags) of final volume in the drug product bag. The resuspended cells are (b) (4)

(b) (4)

Visual inspection is performed by trained operators assessing the filled cryopreservation bag(s) prior to cryopreservation for defects such as bag integrity, visible particulates, and cell clumps using a calibrated inspection station against (b) (4)

Each bag is placed in a transparent (b) (4)

(b) (4)

No (b) (4) (defined as periods without processing greater than (b) (4) are utilized in the lovo-cel manufacturing process.

Shipping

lovo-cel in the metal cassette is placed in a holder and placed into the liquid nitrogen vapor phase of the qualified cryoshipper. Up to four bags of DP for one patient are packed in the same cryoshipper. The cryoshipper is qualified to maintain a temperature of $\leq -140^{\circ}\text{C}$ throughout the duration of shipment (see section 3.2.P.3.5 for shipping validation). Upon receipt at the treatment center, lovo-cel is required to be stored at $\leq -140^{\circ}\text{C}$.

Reviewer Comments: *The submission contains detailed descriptions of each lovo-cel DP manufacturing process including general information regarding equipment used during the manufacturing process. Process parameters and in-process controls are in place for the manufacturing process during key process steps. The information provided appears appropriate.*

3.2.P.3.4 Controls of Critical Steps and Intermediates

In-process microbial controls are provided in section 3.2.P.3.5 *Process Validation and/or Evaluation* below.

3.2.P.3.5 Process Validation and/or Evaluation





As previously stated, lovo-cel DS is manufactured and processed into drug product (b) (4) between processing steps. Therefore, drug substance and drug product manufacturing process validation studies are presented together in this section.

Process Performance Qualification (PPQ)

Process validation for lovo-cel drug substance and drug product was executed at (b) (4) following the routine commercial manufacturing process as described in Sections 3.2.S.2.2 *Description of Manufacturing Process* (lovo-cel DS) and Section 3.2.P.3.3 *Description of Manufacturing Process* above.

(b) (4)

(b) (4)



3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)


The applicant lists 16 quality attributes as specifications for lovo-cel DP tested at release and throughout shelf-life. DP endotoxin and sterility methods are compendial, validated, and specification is set at (b) (4) and “no growth” respectively. Both tests are performed at release and at the end of shelf life.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Please refer to section 3.2.P.7 *Container Closure System* for assessment of CCIT

3.2.P.5.4 Batch Analyses

The release testing results under the DMPQ purview met all pre-defined acceptance criteria for Sterility (No Growth) and Endotoxin (b) (4) per kg patient weight or (b) (4)



3.2.P.7 Container Closure System

lovo-cel, the drug product, is comprised of living cells and is manufactured under aseptic conditions. All container closure components and excipients are verified to be sterile before use. A drug product manufacturing in-process sterility test is performed on (b) (4) solution. Final drug product is tested for sterility and endotoxin; samples are aseptically obtained from the final container immediately prior to freezing of the drug product bag. The drug product is stored frozen and does not contain preservatives.

The primary container closure system (CCS) for lovo-cel DP is a sterile, individually packaged, single-use (b) (4) bag manufactured by (b) (4). A secondary package container (transparent (b) (4)), and a tertiary package container (cryocassette) complete the CCS.

The applicant stated that the primary CCS (b) (4) bag has been demonstrated to meet (b) (4) requirements. The bags are steam sterilized by the manufacturer using a (b) (4) that is validated to achieve a sterility assurance level (SAL) of (b) (4). Each bag is pressure tested with (b) (4) by the manufacturer, and any leaks in the body or fittings result in the bag being rejected. The (b) (4) bags are accepted for use at the lovo-cel manufacturing site based on visual inspection and review of vendor certificates for SAL (b) (4). Sterility testing is performed on (b) (4) bag from each lot received (Acceptance criteria: no growth).

The specifications and technical information of the (b) (4) bags are summarized in the table below:

Attribute	Technical Specification
Bag material	(b) (4)
Spike port with septum, protected with FEP cover	
Inlet tubing	
Female Luer	
Pinch clamp	
Inside bag dimensions	
Outside bag dimensions (including spike port and label pouch)	
Working temperature	
(b) (4)	

Container Closure Integrity Testing

CCIT was performed using (b) (4) method. For the (b) (4) method, the (b) (4) bags were filled with a representative volume of (b) (4)

[REDACTED]

(b) (4)

[REDACTED]

Reviewer Comments: The applicant performed CCIT using the (b) (4) method. The results of both positive controls and bacteriostasis controls demonstrate the suitability of the described CCIT method. The firm determined sensitivity of the CCIT to be (b) (4) defect size. The container closure system and tests appear acceptable.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data









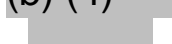
The submitted stability data under DMPQ purview met all acceptance criteria, including Sterility (acceptance criteria: No Growth) and Endotoxin (Acceptance criteria: (b) (4))

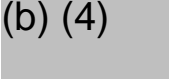




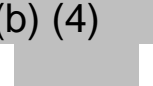




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






In long term stability studies and in (b) (4) stability testing, Sterility and Endotoxin are tested at release and end of shelf-life.











3.2.A APPENDICES




The following table includes a full listing of all facilities associated with the manufacturing and testing of lovo-cel.

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Is this a CMO?	Comments
Facility: (b) (4)    DS manufacturing and in-process testing, DP manufacturing, labeling, packaging, storage, in-process, release and stability testing	Inspection	Yes	Yes	Yes	DMPQ PLI (b) (4)  VAI
Facility: (b) (4)     BB305 LVV manufacturing: purified bulk intermediate, in-process testing, fill/finish and in-process, release testing, BB305 LVV Working cell bank storage	Inspection	Yes	Yes	Yes	DMPQ PLI (b) (4)  NAI

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Is this a CMO?	Comments
Facility: (b) (4)   DP release and stability testing, BB305 LVV in- process, release, and stability testing	Waiver	Yes	Yes	Yes	ORA/OBPO Inspection (b) (4)  NAI
Facility: (b) (4)   DP release and stability testing, BB305 LVV release and stability testing	Waiver	Yes	Yes	Yes	ORA/OBPO Inspection, (b) (4)  NAI
Facility: (b) (4)    DP release and stability testing	Waiver	Yes	Yes	Yes	ORA/OPQO Inspection, (b) (4)  NAI

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Is this a CMO?	Comments
Facility: (b) (4)   DP release and stability testing	Waiver	Yes	Yes	Yes	ORA OPQO MRA Inspection Review of (b)(3), (b)(4)  Surveillance (b)(3), (b)(4)  VAI
Facility: (b) (4)   BB305 LVV release testing	Not required	No	Yes	Yes	
Facility: (b) (4)    BB305 LVV release testing	Not required	No	Yes	Yes	

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Is this a CMO?	Comments
Facility: (b) (4)     BB305 LVV release testing	Not required	No	Yes	Yes	
Facility: (b) (4)    BB305 LVV stability testing	Not required	No	Yes	Yes	
Facility: (b) (4)    BB305 LVV in- process and release testing	Not required	No	Yes	Yes	

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Is this a CMO?	Comments
Facility: (b) (4)    BB305 LVV storage	Not required	No	No	Yes	

3.2.A.1 Facilities and Equipment: (b) (4) -
BB305 Lentiviral Vector Manufacturing

(b) (4) 







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