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CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125806

marnetegrane autotemcel – KRESLADI

**Jared Greenleaf, Consumer Safety Officer, OCBQ/DMPQ/MRB1
Phillip Thai, Consumer Safety Officer, OCBQ/DMPQ/MRB1**

1. **BLA#:** STN 125806/0
2. **APPLICANT:** Rocket Pharmaceuticals, Inc., US License Number 2328
3. **PRODUCT NAME/PRODUCT TYPE**
Non-Proprietary/Proper/USAN: marnetegrane autotemcel
Proprietary Name: KRESLADI
4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**
 - a. **Pharmacological category**
Gene therapy
 - b. **Dosage form**
Suspension
 - c. **Strength/Potency**
(b) (4) × 10⁶ CD34+ cells/kg
 - d. **Route of administration**
Intravenous infusion
 - e. **Indication(s)**
Treatment of severe leukocyte adhesion deficiency type 1

5. MAJOR MILESTONES

Received Resubmission: September 26, 2025

ADD: March 26, 2026

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Jared Greenleaf, CSO, OCBQ/DMPQ/MRB1	3.2.S.2.4 Control of Critical Steps and Intermediate [LV-RP-L201, (b) (4)] 3.2.S.4.1 Specifications [LV-RP-L201, (b) (4)] 3.2.S.4.2 Analytical Procedures [LV-RP-L201, (b) (4)] 3.2.S.4.3 Validation of Analytical Procedures [LVRP-L201, (b) (4)] 3.2.S.6. Container Closure Systems [LV-RPL201, (b) (4)] 3.2.S.7.2 Post Approval Stability Protocol and Stability Commitment [LV-RP-L201, (b) (4)]
Phillip Thai, CSO, OCBQ/DMPQ/MRB1	3.2.P.5.4 Batch Analyses 3.2.P.8 Stability

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
June 14, 2024	Complete Response Letter (CRL)	CRL identifying 11 chemistry, manufacturing, and controls (CMC) deficiencies
June 25, 2024	Teleconference	Informal meeting with applicant to discuss deficiencies
July 08, 2024	Teleconference	Type A meeting to discuss the CRL
October 01, 2024	STN 125806/0.78 (response to CRL on June 14, 2024)	Sponsor submission response to 11 CMC deficiencies. Initial CRL response was deemed incomplete. (reviewed)
December 10, 2024	Teleconference	Type A meeting to discuss the CRL (drug product shelf life and sterility test method validation)
September 26, 2025	STN 125806/0.82 (response to CRL on June 14, 2024 and incomplete response letter on October 15, 2024)	Sponsor submission of response to 11 CMC deficiencies (supersedes STN 125806/0.78) (reviewed)
November 12, 2025	STN 125806/0.87	Update to DP stability data (reviewed)
December 30, 2025	STN 125806/0.89 (response to IR on December 19, 2025)	IR regarding (b) (4) sterility failure (reviewed)
January 20, 2026	STN 125806/0.92 (response to IR on January 12, 2026)	IR regarding shipping method for LVV (b) (4) samples (reviewed)
January 22, 2026	STN 125806/0.94	Update to DP stability data (reviewed)
February 12, 2026	STN 125806/0.99 (response to IR on February 10, 2026)	IR regarding PMC for LVV shipping validation and CCIT (reviewed)
February 18, 2026	STN 125806/0.100 (response to IR on February 17, 2026)	IR confirming PMC language (reviewed)

8. REVIEWER SUMMARY AND RECOMMENDATION**A. EXECUTIVE SUMMARY**

Rocket Pharmaceuticals submitted Biologics License Application (BLA) 125806/0 to support licensure of KRESLADI (marnetegrane autotemcel), an autologous cell therapy intended to treat severe leukocyte adhesion deficiency type-I (LAD-I).

Due to unresolved deficiencies regarding information submitted to original BLA 125806/0, the firm was issued a Complete Response (CR) letter on June 14, 2024. The firm responded to the CR letter with a resubmission on October 1, 2024 (STN 125806/0.78). However, the resubmission was determined to be incomplete, and an incomplete response letter (IRL) was issued on October 15, 2024.

In response to the IRL issued on October 15, 2024, the firm resubmitted its BLA on September 26, 2025 (STN 125806/0.82). In the resubmission, the firm addressed the Division of Manufacturing and Product Quality's (DMPQ) CR additional items, items #10 and item #11. The CR items are summarized below.

- Item #10: During the initial BLA review, the firm provided a lentiviral vector (LVV) (b) (4) validation that was found to be inadequate, because the vector was not used during the study. The firm agreed to execute an additional (b) (4) validation using the LAD LVV. Review of the (b) (4) validation is provided in this memo in Section 3.2.S Drug Substance.
- Item #11: The firm agreed to perform an additional container closure integrity test (CCIT) method validation due to deficiencies in the CCIT method validation initially provided (e.g., lack of a positive control with defect of known size). Review of the CCIT method validation and associated supportive data is provided in this memo in Section 3.2.S Drug Substance.

Additionally, the BLA resubmission on September 26, 2025 (STN 125806/0.82) included drug product batch and stability data using the sterility test method proposed in the original BLA that was deemed inadequate, and therefore, the sterility data was not reliable as communicated in the IRL that was issued October 15, 2024. Review of drug product batch and stability data using a validated sterility test method is provided below in Section 3.2.P.5.4 Batch Analyses and 3.2.P.8.2 Stability.

See the CR letter and the DMPQ review memo uploaded to CBER Connect on June 14, 2024, for additional information.

B. RECOMMENDATION

I. APPROVAL

Based on the information submitted provided in the original application and amendments, DMPQ recommends approval of marnetegravene autotemcel (KRESLAD), with inspectional recommendations and postmarketing commitments.

The LAD LVV will be manufactured at (b) (4)

The LV-34-RP-L201 DS and DP will be manufactured and labeled at (b) (4)

The approval includes an inspectional recommendation for (b) (4). CBER understands the following inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion:

1. To review the new smoke studies to verify the airflow patterns within the (b) (4) that were reperformed in accordance with CAPA 23055/B to implement a more (b) (4) study approach.

The approval also includes a postmarketing commitment:

- Rocket Pharmaceuticals, Inc. commits to conduct an additional shipping validation study, under worst-case conditions, with container closure integrity testing (CCIT) of the (b) (4) performed post-shipping. CCIT will be performed via the (b) (4) method. The firm agrees to provide the validation study report to the Agency as a “Postmarketing Commitment – Final Study Report” by August 30, 2026.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Jared Greenleaf, CSO, OCBQ/DMPQ/MRB1	Concur	
Phillip Thai, CSO, OCBQ/DMPQ/MRB1	Concur	
Kathleen Jones, Branch Chief, OCBQ/DMPQ/MRB1	Concur	
Anthony Lorenzo, Acting Division Director, OCBQ/DMPQ	Concur	

Module 3

3.2.S DRUG SUBSTANCE [Lentiviral Vector]

The lentiviral vector (LVV) used to manufacture the RP-L201 drug product (DP) is identified as LV-RP-L201. LV-RP-L201 is defined as a VSV-G pseudotyped self-inactivating lentiviral vector derived from HIV-1 (family, retroviridae; subfamily, lentivirus) carrying the therapeutic *ITGB2* cDNA. The (b) (4) LVV is (b) (4)

(b) (4) The finished LVV is stored at a recommended temperature of (b) (4).

In amendment STN 125806/0.82, Rocket provided a response to Complete Response Letter item #10 and item #11. Review of the material provided by Rocket to address these deficiencies, as well as review of additional updates, is provided below.

3.2.S.2.4 Control of Critical Steps and Intermediate [LV-RP-L201, (b) (4)]

Rocket provided the following (b) (4) validation study to address item #10 in the Complete Response Letter.

- (b) (4)

(b) (4)

(b) (4)

3.2.P Drug Product [RP-L201]

The DP consists of autologous hematopoietic stem cells transduced with the lentiviral vector (Chim-CD18-WPRE LV), which encodes for the human ITGB2 gene. The DP is a cell suspension for immediate infusion and consists of (b) (4) viable cells/mL of LV-34-RP-201 (KRESLADI, genetically modified hematopoietic stem cells/DS to express the human ITGB2 gene), (b) (4) (cryo-preservative). The DP is sterile in an (b) (4) 50 mL ethyl vinyl acetate bag, which includes three-way split, luer-activated needle-free injection ports (two female and one male), and sterile-weldable tubing. Each bag is filled with 30 mL of DP intended for intravenous infusion. KRESLADI is supplied as a cryopreserved product and is stored and shipped at $\leq -150^{\circ}\text{C}$. The DP does not contain any anti-microbial agent.

3.2.P.5.4 Batch Analyses

According to amendment STN 125806/0.82, (b) (4) post-PPQ batches were manufactured at the commercial manufacturer, (b) (4). The specifications include:

- Endotoxin (b) (4)
- Sterility: no growth
- Visual inspection: labels complete and accurate, free of visible leaks, essentially free of foreign matter, and bag intact and undamaged

All batches met the specification for endotoxin, sterility, and visual inspection except for batch (b) (4), which showed growth for the (b) (4) sterility test. Sterility testing for (b) (4) showed no growth for the same batch. Rocket initiated an investigation at the testing site (b) (4) and manufacturing site, which resulted in no definitive root cause with man and method. The applicant considered the contributing factors were from open manipulations and sample transport in non-classified areas.

In amendment STN 125806/0.89, Rocket provided all reports and data associated with batch (b) (4), whose (b) (4) failed sterility. The documents provided by the applicant included the deviation investigation report, batch manufacturing record, environmental monitoring (EM) data, personnel monitoring, list of equipment used and their calibration dates, (b) (4) cleaning documents, materials

transfer records through the manufacturing facility, as well as (b) (4) sterility testing and investigation reports for the affected (b) (4) sterility failure.

Rocket states that all open manipulations occurred in the Grade (b) (4) environment according to the batch record. There were no deviations to aseptic manipulation methods, which were executed according to (b) (4) established procedures. All personnel involved were trained and qualified to perform the assigned tasks, including all Grade (b) (4) operators and verifiers. All materials were introduced into the Grade (b) (4) environment according to (b) (4) established procedure. Sampling for sterility testing was performed according to established procedure without any method deviation. No errors were identified related to sample collection, delays, spillage, mishandling, or aseptic breaches.

Rocket states the facility, specifically the cleanroom (b) (4) was in a state of control. All viable and non-viable EM results as well as differential pressure, temperature, and humidity were within specification. There were no alert or action level excursions for personnel monitoring and no deviations noted related to the gowning process. (b) (4) cleaning was performed as outlined in (b) (4) manufacturing area cleaning procedure with all pre-checks, pre-cleaning, and post-cleaning performed.

Rocket claims that no root cause was identified as there were no systemic deficiencies or procedural failures within the manufacturing and testing processes. The applicant identified potential contributing factors (man and method) with low-level risk associated with the open sample manipulation in the Grade (b) (4) environment and the potential for contamination during transport or handling in non-classified areas.

In amendment STN 12806/0.92, Rocket provided information on actions taken in the event of a positive sterility result during the Kresladi manufacturing process. The firm outlined stepwise processes that escalate the out of specification (OOS) event from initiating a batch hold to the removal of the batch by the firm's Quality Unit according to the established disposition procedure (in the event the OOS investigation confirms the original sterility result as 'growth').

Reviewer's comment: The DP lots met the specifications for sterility, endotoxin, and visual inspection, except for sterility for batch (b) (4). The information provided in amendment STN 125806/0.89 regarding the (b) (4) sterility failure appears acceptable. The firm provided comprehensive reports and testing results to support the claim that (b) (4) facility, equipment, personnel, and process appear to be in a state of control and no deviations occurred that could potentially contribute to the positive sterility result for (b) (4). Rocket also stated that no open manipulation occurred in non-classified areas and that the initial statement in STN 125806/0.82 (the applicant considered the contributing factors were from open manipulations and sample transport in non-classified areas) was unclearly written. There appears to be low patient safety risks associated with this deviation as all other sterility tests resulted in 'no growth' and that (b) (4) was manufactured for stability purposes only and is not intended for patient use.

The information provided in amendment STN 12806/0.92 regarding controls and actions taken to prevent distribution of products that fail sterility appears acceptable. The firm's actions according to their established procedures appear appropriate to ensure patient safety in the event of microbial contamination.

It is noted that all samples tested for sterility (b) (4) for KRESLADI (b) (4) final drug product) are stored frozen (in LN₂ (b) (4) before testing at the commercial testing facility. Sterility testing of frozen samples can potentially yield false negative outcomes due to potentially suppressed microbial growth and increased microbial death at low temperatures. The effectiveness of sterility testing of frozen samples is deferred to the Office of Therapeutic Products (OTP). All other data not germane to microbial control are deferred to OTP.

3.2.P.8 Stability

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

In amendments STN 125806/0.82 and 125806/0.87, Rocket updated their stability program using (b) (4) health donor (HD) batches manufactured at (b) (4) to update the drug product (DP) expiry (three months DP shelf-life when stored at $\leq -150^{\circ}\text{C}$). The originally proposed expiry was (b) (4) months (proposed in amendment 125806/0.70). The (b) (4) HD batches covered the proposed cell concentration ranges (b) (4)

The (b) (4) batches were filled in (b) (4) bags, which are representative of the commercial container closure (b) (4) bag). The (b) (4) HD batches are stored at the intended storage temperature of $\leq -150^{\circ}\text{C}$ and are monitored for stability for all critical quality attributes (CQA), which includes sterility.

(b) (4) DP batch (b) (4) was manufactured and filled into a (b) (4) bag to demonstrate the container closure's ability to maintain sterility during storage throughout shelf-life. This batch is intended to only be tested for sterility, endotoxin, and mycoplasma at time points 0 (release) and (b) (4) months.

Rocket initially manufactured (b) (4) other (b) (4) batches. The (b) (4) batches (b) (4) failed to meet cell concentration specification due to (b) (4) (targeted (b) (4) cells/mL at formulation) and poor sample recovery post-thaw (target specification is (b) (4) cells/mL). All other release attributes tested on these batches met specifications aside from the concentration; however, these (b) (4) batches were not included in the post-PPQ stability program.

In amendment STN 125806/0.94, Rocket updated the stability data for the (b) (4) post-PPQ HD DP batches from the latest CRL resubmission (STN 125806/0.82) and proposed a six-month expiry.

Table: Summary of Stability Batches

Batch	Date of Manufacture	Storage Temperature	Data available	Storage Container
(b) (4)	(b) (4)	≤ -150 °C	(b) (4) months	(b) (4)
(b) (4)	(b) (4)	≤ -150 °C	(b) (4) Months	(b) (4)
(b) (4)	(b) (4)	≤ -150 °C	6 Months	(b) (4)
(b) (4)	(b) (4)	≤ -150 °C	6 Months	(b) (4)

Reviewer's comment: The stability information appears acceptable for the post-PPQ HD DP batches. The DP lots filled in the (b) (4) bag (b) (4) met the specifications for the sterility, endotoxin, mycoplasma, and appearance at release (T0) and at T3. Lot (b) (4) filled in the (b) (4) met specifications for sterility, endotoxin, and mycoplasma at T0 and at (b) (4). The stability/sterility information to date appears to support Rocket's initially proposed three-month expiry when stored at ≤ -150 °C.

The use of the (b) (4) bags for stability-related purposes of facilitating multiple timepoint testing appears acceptable. The features of the (b) (4) bags appear to be representative or worst-case of the proposed commercial final container closure system (b) (4) bags). Although the (b) (4) bag has a different configuration compared to the intended container closure system (b) (4) bags), it is from the same manufacturer, is composed of the same material (ethylene vinyl acetate), and features a similar surface to volume ratio. The (b) (4) bags feature additional sample ports, which appear to be worst-case as they present additional failure points for container closure integrity as compared to the (b) (4) bags.

In amendment STN 125806/0.94, the applicant proposed a six-month expiry. To support that, they provided passing sterility data at (b) (4) months for the lot filled at (b) (4) into the proposed commercial final container (b) (4). Additionally, passing sterility data at three months was provided for (b) (4) lots filled into the (b) (4) bags.

As the DP is stored at ≤ -150 °C the major risks to the integrity would be freezing and handling of DP bags. Rocket provided container closure integrity testing (CCIT) data that was performed on the (b) (4) bags by (b) (4) in (b) (4) (see original BLA DMPQ review memo for detailed CCIT review). These bags were filled at Rocket with (b) (4)

(b) (4) storage in LN₂. The filling parameters were (b) (4) to the proposed commercial process, including the (b) (4)

All bags remained integral after shipping. As these 510(k)-cleared

bags are designed for cryopreservation, short-term freezing and shipping should be worst-case compared to long-term freezing only.

While sterility data was not provided for (b) (4) lots at six months, the supportive CCIT data after worst-case conditions as well as the sterility data from (b) (4) lots at three months in the (b) (4) bag and (b) (4) months in the (b) (4) bag indicates that the risk to allowing a 6-month expiry in a 510(k)-cleared bag is low, especially when the DP is stored at $\leq -150^{\circ}\text{C}$. However, we defer the final decision on expiry to OTP. Additionally, all other stability results pertaining to product quality attributes and not germane to microbial control are deferred to OTP.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The sponsor commits to completing the stability studies listed in 3.2.P.8.1. The sponsor also committed to placing a minimum of (b) (4), on stability at $\leq -150^{\circ}\text{C}$ according to their stability protocol provided that at least (b) (4) is manufactured. The batches will be tested using the approved methods and acceptance criteria in place at the time of stability testing. The stability batches will be filled in (b) (4) bags due to the material requirements and manipulations necessary to perform stability studies with multiple timepoints.

Reviewer's comment: *The post-approval stability commitment appears acceptable. Due to the nature of testing multiple timepoints throughout the stability study, the use of (b) (4) bags, which allow for the sampling of multiple timepoints also appear acceptable to ensure sterility throughout the shelf-life. All product quality attributes are deferred to OTP.*