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CBER CMC BLA Review Memorandum

BLA STN 125806

**marnetegrane autotemcel
KRESLADI**

Reviewers

Pankaj K. Mandal, PhD, OTP/OCTHT/DCT2/TVBB

Andrew Timmons, PhD, OTP/OGT/DGT2/GTB5

Sukyoung Sohn, PhD, OTP/OGT/DGT1/GTB1

Athena Russell, PhD, OTP/OGT/DGT2/GTB5

1 Introductory Information

1.1 BLA#: STN 125806

1.2 Applicant name and license number

Rocket Pharmaceuticals Inc.

U.S. License # 2328

1.3 Product name and type

Non-proprietary/Proper/USAN	marnetegrane autotemcel
Proprietary Name	KRESLADI
Company Codename	LV-34-RP-L201
UNII Code	RD86XHH46N
NDC Code	83537-034-01

1.4 General description of the final product

Pharmacological category	autologous hematopoietic stem cell-based gene therapy
Dosage form	Cell suspension for infusion
Strength/Potency	0.34 E+06 – 6.1E+06 cells/mL (0.32 E+06 – 6.1E06 CD34+ cells/mL) with a minimum recommended dose of > 2.8E+06 CD34+ cells/kg body weight.
Route of Administration	Intravenous infusion
Indication	For the treatment of pediatric patients with severe leukocyte adhesion deficiency-I (LAD-I), due to biallelic variants in ITGB2 without an available human leukocyte antigen (HLA)-matched sibling donor for allogeneic hematopoietic stem cell transplant.

1.5 Major milestones

Original BLA Submission	1-Aug-2023
Major Amendment	12-Feb-2024
Complete Response Letter Sent	14-Jun-2024
Incomplete Response Letter Sent	15-Oct-2024
Complete Response Resubmission	26-Sep-2025
Filing letter sent	10-Oct-2025
PDUFA action due date	28-Mar-2026

1.6 CMC/Quality Review Team

Reviewer/Affiliation	Initials	Section/Subject Matter
Pankaj K. Mandal, PhD, OTP/OCTHT/DCT2/TVBB	PKM	BLA Chair, DP Manufacturing Process
Andrew Timmons, PhD, OTP/OGT/DGT2/GTB5	AET	LVV specifications, CD11a clinical assay validation
Sukyoung Sohn, PhD, OTP/OGT/DGT1/GTB1	SS	LVV and DP Stability
Athena Russell, PhD, OTP/OGT/DGT2/GTB5	ALR	DP and LVV analytical assays and validations
Andrey Sarafanov, PhD, OTP/OPPT/DH/HB2		Leachables and extractables (consult)

1.7 Inter-center consults requested

None

1.8 Submission(s) reviewed

Date Received	BLA-125806/0.###	Comments/Status
30-Sep-2024	78	Response #1 to CRL (incomplete)
26-Sep-2025	82	BLA resubmission
3-Oct-2025	83	Response to CMC IR #1
7-Nov-2025	86	Response to CMC IR #2
18-Dec-2025	88	Response to CMC IR #3
16-Jan-2026	91	Response to CMC IR #4
23-Jan-2026	95	Response to CMC IR #5
27-Jan-2026	96	Response to CMC IR #6
10-Feb-2026	97	Response to CMC IR #7
24-Feb-2026	103	Response to CMC IR #9
25-Feb-2026	105	Response to CMC IR #10
02-Mar-2026	108	Response to CMC IR #11
19-Mar-2026	115	Response to FDA IR related to Non-506B PMCs
24-Mar-2026	117	Response to CMC IR #13
24-Mar-2026	118	Response to FDA IR related to Accelerated Approval PMRs
25-Mar-2026	122	Final agreement on Accelerated Approval PMRs

1.9 Referenced regulatory submissions (e.g., IND BLA, 510K, Master File, etc.)

Submission type & #	Referenced Item	Holder	Letter of Cross-Reference	Comments/Status
MF (b) (4)	(b) (4)	(b) (4)	Included with original submission	Active, letter of authorization (LOA) for section 3.2 A Appendices and 3.2.A.1 Facilities and Equipment.
MF (b) (4)	DP lot release assays	(b) (4)	Included in original submission	Active, LOA authorizes incorporation of information contained in the MF by cross-reference.
MF (b) (4)	(b) (4)	(b) (4)	Included in original submission	Active
MF (b) (4)	(b) (4)	(b) (4)	Included in the BLA	Active

Reviewer's comment: incorrect Letter of authorization (LOA) was submitted for (b) (4). In response to CMC IR #11 (Amendment 125806/0.108, submitted 02-Mar-2026), the Applicant submitted the correct LOA for (b) (4). Review of (b) (4) was conducted as part of the original BLA review.

2 Reviewer Summary and Recommendation

2.1 Executive Summary of BLA Resubmission

Upon review of the resubmission of BLA-125806 received on 26-Sep-2025 (Amendment 125806/0.82), the FDA CMC review team concludes that the described manufacturing process, test methods, and control measures for marnetegrane autotemcel (marne-cel; KRESLADI) are capable of generating autologous products with consistent quality attributes, in a manner that satisfies the statutory requirements for commercial manufacture and sale of KRESLADI in the United States.

At the time of the administrative due date (ADD; June 30, 2024) for the original BLA submission (received by the FDA on 01-Aug-2023), four outstanding quality deficiencies prevented the approval of BLA-125806. These deficiencies (outlined in **Section 3.1** of this review) pertained to microbial control of the lentiviral vector (LVV), long-term stability of the KRESLADI, and the analytical method used to establish the dose and strength of the KRESLADI. In the BLA resubmission received on 26-Sep-2025, the Applicant provided additional validation reports and additional stability datasets, which resolve the approvability issues identified in the initial review of BLA-125806.

Product Description

KRESLADI is composed of autologous, enriched CD34+ cells, which have been stably transduced with the LVV (LV-RP-L201) expressing an intact copy of the *ITGB2* gene. In transduced cells, expression of *ITGB2* is driven by a chimeric promoter consisting of human Cathepsin G (b) (4) retroviral promoter sequences.

Therapeutic Rationale

Progeny leukocytes derived from genetically modified CD34+ cells express a functional copy of *ITGB2*, which permits the formation of functional $\beta 2$ integrin complexes (CD18/CD11 heterodimer) and the rescue of leukocyte trafficking and localization to sites of infection. Importantly, because the therapeutic copy of *ITGB2* is stably integrated into the genome of genetically modified CD34+ cells, a single treatment with KRESLADI is intended to provide lifelong clinical benefit.

Manufacturing and Quality

The manufacture of KRESLADI involves the transduction of enriched, autologous CD34+ cells with the LV-RP-L201 LVV. This LVV is an HIV-1 based 3rd generation, self-inactivating, vesicular stomatitis virus glycoprotein (VSV-G) pseudotyped LVV encoding the *ITGB2* gene.

The LV-RP-L201 LVV is manufactured by a contract manufacturer (b) (4)

The starting material for KRESLADI manufacture consists of autologous CD34+ cells isolated from G-CSF and plerixafor mobilized peripheral blood apheresis material. Mobilized CD34+ cells are collected by leukapheresis at qualified treatment centers and are shipped to the site of KRESLADI manufacture (b) (4)

(b) (4) Here, mobilized peripheral blood cells are

(b) (4) at a nominal concentration of $3.4E+05$ to $6.1E+06$ viable cells per mL to form the (b) (4) RP-L201 drug product (DP). The (b) (4) DP is then dispensed into (b) (4) 50 mL EVA bags at a nominal fill volume of 30 mL. The filled bags are then labeled, frozen in a (b) (4), and cryopreserved at $\leq -150^{\circ}\text{C}$ to await shipment back to the treatment center. The shelf life of

KRESLADI is 6 months at $\leq -150^{\circ}\text{C}$. KRESLADI is shipped to the treatment center in a qualified cryogenic shipper. At the treatment center, KRESLADI is thawed and administered via intravenous infusion following myeloablative therapy. The maximum allowable in-use hold duration for DP at room temperature from the start of thaw to completion of infusion is 30 minutes.

CMC flexibilities

While the September 26, 2025, BLA resubmission resolves the outstanding approvability concerns, the FDA has extended regulatory flexibility in several areas of the CMC review, given that LAD-I is a rare genetic immunodeficiency with high mortality in young children. Given the intractable nature of this disease and the importance of ensuring access to etiological treatment, the FDA has accepted certain aspects of the quality control strategy that would typically require further refinement in less severe conditions. As such, the FDA will allow additional information to be provided post-licensure as post-marketing commitments to fulfil these aspects while providing patient access. The FDA has exerted regulatory flexibility with respect to the design, execution, and interpretation of long-term stability and in-use stability studies. Specifically, as indicated in the Type A written response sent on December 10, 2024 (Amendment 125806/0.79), the FDA agreed to consider long-term stability data generated in a representative, small-format container closure as opposed to requiring the use of the commercial container closure as described in 21 CFR 211.166(a)(4). The FDA agreed to this flexibility due to the challenges associated with generating stability data in the primary container closure given the large volume required for samples obtained from human subjects, as well as the totality of supportive evidence generated during the RP-L201-0318 clinical study. Additionally, the maximum allowable in-use hold duration of up to 30 minutes for KRESLADI at room temperature was determined based on historical in-use hold time data during the clinical study and limited in-use stability data from one lot. The FDA agreed to this flexibility considering the adequate in-use stability study plan provided in this resubmission, limited data from one lot, and the totality of supportive evidence generated during the clinical study. An additional in-use stability study will be performed as a PMC to further support the in-use conditions for KRESLADI. In addition to DP stability, regulatory flexibility was also applied to accept the LVV stability data in support of an (b) (4) shelf life for LV-RP-L201 when stored at (b) (4), based on the totality of stability data from (b) (4) LVV lots and consideration of assay variability.

The FDA also exerted regulatory flexibility with regard to quality control, process performance qualification (PPQ), and inspectional evaluation of the LV-RP-L201 LVV. Specifically, in several instances the FDA agreed that the Applicant may leverage assay validation data generated with an alternative LVV ((b) (4)) in lieu of requiring that assay validation data be generated with the LV-RP-L201 drug substance. Further, during the inspection of the LVV manufacturing facility (b) (4); inspection dated (b) (4), the FDA observed the manufacture of (b) (4) in lieu of the LV-RP-L201 vector. Of note, this regulatory flexibility was underpinned by the high degree of similarity between

LV-RP-L201 and (b) (4), which was detailed in response to the 27-Oct-2023 information request conveyed during the initial review period.

The FDA has also exerted regulatory flexibility with regard to the PPQ strategy for the KRESLADI drug product. Specifically, the FDA accepted the retrospective inclusion of the final clinical drug product lot (lot (b) (4)) into the PPQ program for KRESLADI, given that the PPQ program executed by the Applicant includes (b) (4) PPQ lots manufactured with healthy donor starting material.

2.2 Review team recommendation

The FDA CMC review team concludes that this biological license application (BLA) provides an adequate description of the manufacturing process and characterization of marnetegrane autotemcel (KRESLADI). The CMC review team has also concluded that the manufacturing process along with the associated test methods and control measures, and in conjunction with the listed post marketing requirements and commitments, are capable of yielding a product with consistent quality characteristics.

Following the review of the original BLA submitted on 1-Aug-2023, several deficiencies were identified, as outlined in Section 3.1. Following internal discussion, and in the context of the urgent need of patients, the FDA determined that certain deficiencies (deficiencies 1, 2, 4, and 5) must be addressed prior to licensure, and that the remaining deficiencies (deficiencies 3, 6, 7, 8, and 9) may be addressed following licensure through post-marketing commitments.

The Applicant has acceptably addressed the four deficiencies which must be resolved prior to licensure. Further, the Applicant has acceptably responded to the remaining deficiencies, which may be resolved in a post-licensure setting. Specifically, the Applicant has provided either new empirical data or acceptable protocols which may be completed as post-marketing commitments (PMCs).

This information along with PMCs and a post-marketing requirement (PMR) listed below satisfy the CMC requirements for biological licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacturing and sale of biological products. Based on the information provided in the BLA submission and subsequent amendments, the CMC review team recommends approval of this BLA.

CMC post-marketing requirement (PMR) and post-marketing commitment (PMC):**CMC PMR under Accelerated Approval**

2. Submit data from supplemental validation studies performed on the LAD-1 Flow Cytometry assay described in SOP-778817. This validation is needed to enable data interpretation of your confirmatory study and specifically evaluate the performance of the CD18 (6p7) and CD11a assays throughout the complete analytical range, including low cell surface expression levels, and should include assessments of repeatability, linearity, accuracy, intermediate precision, and specificity.

Study Milestone dates:

- Final Protocol Submission: July 31, 2026
- Study Completion: December 31, 2026
- Final Study Report Submission: February 27, 2027

CMC PMR under Section 505(o)

4. An adequate leachables safety assessment for KRESLADI through its manufacturing process, storage, and in-use conditions. This assessment must include the following:

- a. Assessment of both organic and elemental extractables from the high-risk for leachables manufacturing/storage components of final DP (i.e., cumulative leachables in DP).
- b. The leachables study can be conducted by simulating the DP manufacturing process from the step with high-risk for leachables components (b) (4)

performed using maximal hold times and temperatures through the process, product freezing, shelf-life storage, thawing, and in-use processing.

- c. This evaluation must include a full toxicological risk assessment for the identified leachables.

Study milestone dates:

- Final Protocol Submission: June 30, 2026
- Study Completion Date: December 31, 2026
- Final Study Report Submission: May 31, 2027

PMCs

5. Rocket Pharmaceuticals, Inc. commits to conducting an additional in-use stability study to support in-use conditions for KRESLADI from the start of thaw to completion of infusion as described in the approved USPI. The final study report will be submitted as a “Postmarketing Commitment – In-use Stability Final Study Report” by September 30, 2026, and revise the hold duration in the USPI as supported by the in-use stability data.
6. Rocket Pharmaceuticals, Inc. commits to provide a risk assessment and perform additional studies to evaluate the impact of changes to (b) (4)
[REDACTED]
[REDACTED] The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by March 31, 2027.
7. Rocket Pharmaceuticals, Inc. commits to (b) (4)
[REDACTED]
[REDACTED] The final report will be submitted as a “Postmarketing Commitment – Final Study Report” by March 31, 2027.
8. Rocket Pharmaceuticals, Inc. commits to perform a prospective revalidation of the KRESLADI drug product potency assay by (b) (4)
[REDACTED]. The final validation study report will be submitted as a “Postmarketing Commitment – Final Study Report” by March 31, 2027.
9. Rocket Pharmaceuticals, Inc. commits to conduct (b) (4)
[REDACTED]
[REDACTED] The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by September 30, 2026.
10. Rocket Pharmaceuticals, Inc. commits to perform supplemental validation of the (b) (4)
[REDACTED]
[REDACTED] The final validation study report will be submitted as a “Postmarketing Commitment – Final Study Report” by March 31, 2027.
11. Rocket Pharmaceuticals, Inc. commits to conduct additional studies to define the (b) (4)
[REDACTED]

(b) (4). The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by September 30, 2026.

12. Rocket Pharmaceuticals, Inc. commits to conduct additional studies to evaluate whether assay

(b) (4)

The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by March 31, 2027.

13. Rocket Pharmaceuticals, Inc. commits to submit the Insertion Site Analysis (ISA) assay protocol and validation report. The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by March 31, 2027.

14. Rocket Pharmaceuticals Inc. commits to updating Section 14.4 of SOP-778817, which describes the “LAD-1 Flow Cytometry” assay used throughout the RP-L201-0318 clinical study to evaluate the expression of CD18, CD11a, and CD11b on neutrophils from treated patients. The updated Section 14.4 will describe (b) (4)

similar to experiments performed as part of the method validation. The final study protocol will be submitted as a “Postmarketing Commitment – Final Study Protocol” by August 31, 2026.

15. Rocket Pharmaceuticals, Inc. commits to reassessing the acceptance criterion for the (b) (4) assay performed as part of release of the LV-RP-L201 lentiviral vector after additional LV-RP-L201 lots are manufactured and used to generate commercial KRESLADI DP. The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by December 31, 2028.

16. Rocket Pharmaceuticals, Inc. commits to implement storage and shipping of KRESLADI sterility samples at (b) (4), conduct a (b) (4) hold time study for DP lot release and provide data to support (b) (4) sample testing with current validated sterility test method. The final study report will be submitted as a “Postmarketing Commitment” by March 31, 2027.

17. 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 validation study report will be submitted as a “Postmarketing Commitment – Final Study Report” by August 30, 2026.

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Pankaj K. Mandal, Ph.D. Senior Staff Fellow OTP/OCTHT/DCT2/TVBB	Concur	
Andrew Timmons, Ph.D. Senior Biologist OTP/OGT/DGT2/GTB5	Concur	
Sukyoung Sohn, Ph.D. Biologist OTP/OGT/DGT1/GTB1	Concur	
Athena Russell, Ph.D. Staff Fellow OTP/OGT/DGT2/GTB5	Concur	
Nirjal Bhattarai, Ph.D. Chief, Tumor Vaccine and Biotechnology Branch	Concur	
Kimberly Schultz, Ph.D. Director, Division of Gene Therapy 2	Concur	
Denise Gavin, Ph.D. Director, Office of Gene Therapy CMC	Concur	

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3 CMC review of complete resubmission

3.1 Point-by-point review of complete response (CR) items

3.1.1 Complete Response Item #1 – CD34⁺ identity and dose determination assay

Reviewed by ALR

3.1.1.1 Text of CR item

Your application does not contain sufficient information to support validation of the 'CD34⁺ Cell Identity' assay also used for drug product (DP) strength (i.e., dose determination). As described in VR016253-ADD1.R00, the samples used to establish critical validation parameters (e.g., accuracy, precision, linearity) consisted of transduced healthy donor CD34⁺ cells that had either been (b) (4)

[REDACTED] . However, this approach does not adequately evaluate the performance of the assay.

During routine performance of the assay, the CD34⁺ dose determination assay must be capable of accurately identifying and quantifying the frequency of CD34⁺ cells in a mixture of CD34⁺ and CD34⁻ cells. By recapitulating this condition using (b) (4)

[REDACTED] significant sources of variability are unaccounted for in your method validation. Specifically, the impact of (b) (4) of CD34⁻ cells cannot be determined from your method validation.

Importantly, because background staining may artificially inflate the detected number of CD34⁺ cells, this method validation does not provide sufficient assurance that patients receive the intended dose of CD34⁺ cells. Please provide an assay validation for the CD34⁺ dose determination assay in which the assay is validated using (b) (4) methods and test sample representative of routine testing that will be encountered in the commercial assay. To ensure an adequate study design, please provide a draft validation protocol as an amendment to IND 18485 for review prior to initiating this study.

3.1.1.2 Overview of concern

During review of the BLA original submission, the Applicant provided an assay validation report and a validation addendum report for the CD34⁺ cell identity (b) (4) method. Both validation studies were designed inappropriately, and neither study was sufficient to support validation of the CD34⁺ cell identity and dose determination method for commercial release testing. Briefly, (b) (4)

[REDACTED] Furthermore, the validation addendum study was not designed to validate the full analytical range of the assay up to (b) (4) CD34⁺.

3.1.1.3 Firm's response to CR item

The Applicant submitted an additional validation study report (NLGE-13815) in the first resubmission for FDA consideration, along with two draft revalidation protocol designs and a development report (Amendment 125806/0.78; October 1, 2024). This validation study was also deemed insufficient upon review. The two draft protocols for the revalidation study were reviewed and FDA comments were relayed on November 19, 2024, which advised the Applicant to conduct the revalidation study according to *CD34 Flow Validation Protocol Design 1* (Comment 1). Design 1 followed previous FDA advice to conduct the study using validation samples generated from (b) (4), and analyzed exactly as described in the CD34⁺ cell method SOP (SPBT5521). FDA additionally requested a procedure for qualifying new lots of (b) (4) used in the (b) (4) (Comment 6).

In the current resubmission, the Applicant performed several additional development, qualification, and validation studies to support the revalidation of the commercial CD34⁺ cell assay (**Table 1**).

Table 1. Summary of new reports submitted in response to CR letter item #1

Report ID	Report Title	Purpose
VR016253-ADD1.R03	Validation Report Addendum for Identity Assay for Hematopoietic Cells by (b) (4)	Validation addendum report revision containing multiple edits, corrections, and clarifications. Earlier versions of this report (VR016253-ADD1.R00 and VR016253-ADD1.R01) were reviewed with the original BLA submission.
DR016253.ADD2	Feasibility of Revalidation of (b) (4) in the Identity Assay for Hematopoietic Cell by (b) (4)	Development/feasibility studies; (b) (4) studies; confirmation of validation acceptance criteria
DR016253.ADD3	Qualification of Samples Intended for Revalidation of (b) (4) in the Identity Assay for Hematopoietic Cells by (b) (4)	Qualification of (b) (4) samples to be used for re-validation study
VR016253.ADD2	Validation Addendum 2 for Identity Assay for Hematopoietic Cells by (b) (4)	Re-validation of CD34 release test method (b) (4) for commercial use

(b) (4)

10 pages determined to be not releasable: (b)(4)

3.1.2 Complete Response Item #2 – DP shelf life

Reviewed by SS

3.1.2.1 *Text of CR item*

Your application does not contain sufficient information to determine a DP shelf life. You proposed to provide stability data from one DP lot in a final container closure by June 11, 2024. However, analysis of (b) (4) after storage (b) (4) months) in the proposed container closure is insufficient to allow an assessment of DP stability (b) (4). Stability data acquired in an alternative container closure (e.g., (b) (4)) may be used as supportive, but not primary, stability data. In addition, DP stability should include an assessment of potency. To support a commercial shelf life of your DP, please provide long-term stability data from at least three DP lots across the proposed DP cell concentration range, packaged in the commercial container closure, at defined times after storage, to demonstrate that DP critical quality attributes (CQAs; e.g., viability, potency) remain stable over the proposed shelf life. For these DP lots, please also provide sterility data at release and sterility or container closure integrity testing (CCIT) data at the proposed expiry to demonstrate that the product remains sterile throughout the shelf life, and confirm if the volume tested for sterility, if applicable, is in accordance with (b) (4) or submit data to support any volume adjustments. To ensure an adequate study design, please provide the stability study protocol for review as an amendment to IND 18485 prior to initiating the long-term stability study.

3.1.2.2 *Overview of concern*

During review of the original BLA submission, the Applicant did not provide sufficient information to determine a DP shelf life or to confirm sterility at the time of expiration. Multiple deficiencies were identified in the stability program. First, a (b) (4) was used for the primary DP stability studies instead of the final container closure system (b) (4) cryobag), which can only serve as supportive data rather than primary stability data. Second, only (b) (4) process performance qualification (PPQ) DP lots in (b) (4) were placed on the long-term stability program. Third, the study comparing stability in bags versus (b) (4) was insufficient to justify the surrogate use of (b) (4) because it included only (b) (4) data, and demonstrated a (b) (4) and bags. The DP stability issues were communicated to the Applicant from the beginning of the review cycle; however, they were not able to provide data to resolve DP stability issues. As stated in 21 CFR 211.166, stability data from an adequate number of DP lots in the final container closure system at defined time points are expected to support a commercial shelf life. Additionally, because cell concentration can impact cell health post-thaw, stability data are needed to support the range of proposed final DP cell concentrations.

3.1.2.3 Firm’s response to CR item

Per FDA recommendation, the Applicant submitted a stability study plan to IND 18485/80 on July 12, 2024, which was reviewed by FDA with feedback provided on July 23, 2024. After several rounds of communications with the Applicant, FDA agreed with a revised stability protocol in the Type A (Amendment 125806/0.79) written response issued on December 10, 2024, with the stability acceptance criteria remaining under consideration. As agreed upon in the Type A meeting response, a scaled-down container closure system (b) (4) (Figure 1 and Figure 2) was used in the DP stability studies. The (b) (4) bag is made of the same material (ethylene vinyl acetate, EVA) as the final container closure (b) (4) bag and is acceptable for use in the stability study.

Figure 1. Technical Drawings for (b) (4) Bag and (b) (4) Bag

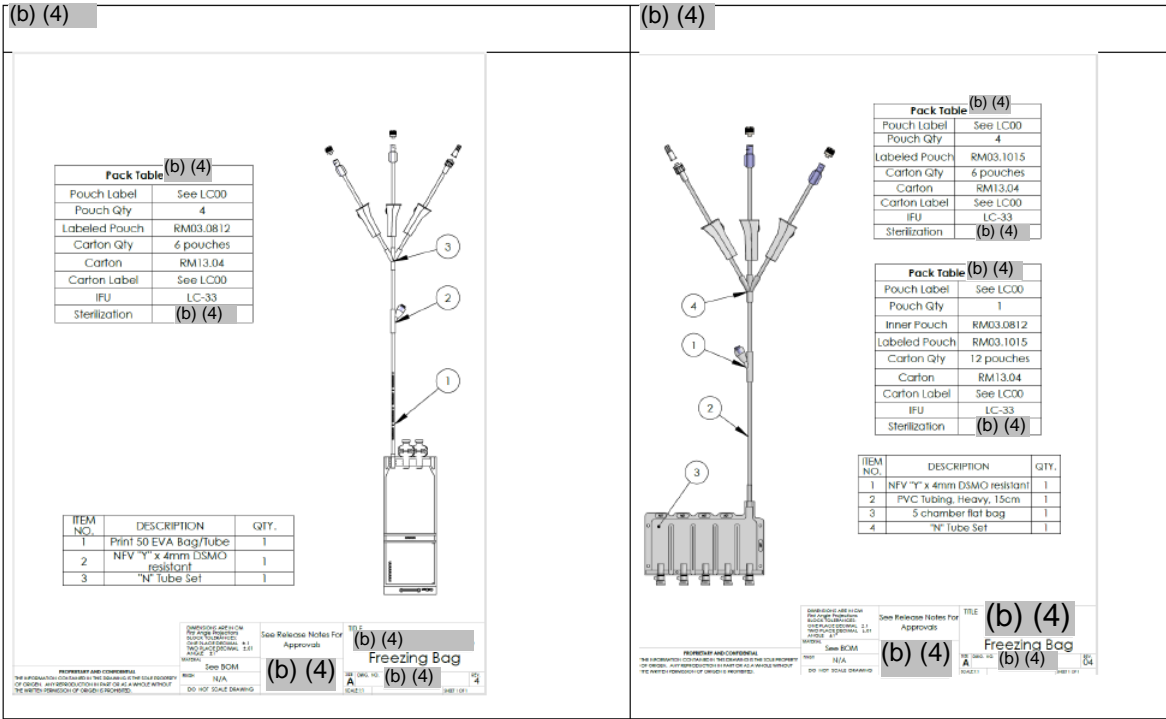


Figure 2. Filling and sealing multi-chamber (b) (4) bags



The Applicant initiated a new stability study following the revised protocol (Table 6) using (b) (4) healthy donor DP lots manufactured at the commercial facility (b) (4) spanning the proposed cell

concentration range: (b) (4)

(b) (4) (Table 8). These (b) (4) lots were packaged in (b) (4) bags. Sterility testing is conducted using DP lot (b) (4) packaged in (b) (4) (Table 7). Refer to the DMPQ review memo for this resubmission for additional details on sterility testing as part of stability study. Post-approval stability studies will be conducted according to the stability protocol outlined in Table 9, with acceptance criteria revised to align with the finalized DP release specification. According to (b) (4) guidance, drug products with a proposed shelf life of (b) (4) months or less is recommended to be tested for long-term stability monthly for the first 3 months, then at 3-month intervals. Although the stability protocol outlined in Table 6 does not include a 2-month timepoint, FDA agreed to this approach as part of regulatory flexibility. This decision was based on the low risk associated with this omission, given the Applicant's acceptable justification regarding the downward trend in (b) (4) observed between the 3-month and 6-month timepoints, as discussed later in this section.

Table 6. RP-L201 DP Long-Term Stability Protocol (b) (4) Bag, ≤-150°C)

Test	Method No.	Acceptance Criteria	Timepoints (Months)				(b) (4)
			0 (Release)	1	3	6	
Total Viable Cell Count	(b) (4)	(b) (4)	X	X	X	X	
Cell Viability			X	X	X	X	
(b) (4)			X	X	X	X	
CD34+ Cell Identity			X	X	X	X	
Viable CD34+ cells/kg*			X	X	X	X	
(b) (4)			X	X	X	X	
(b) (4)			X	X	X	X	
Transduction Efficiency			X	X	X	X	
Neutrophil Adhesion Assay			X	X	X	X	
Visual Appearance***			X	X	X	X	
Mycoplasma			X	NR	X	NR	
Endotoxin			X	NR	X	NR	
Sterility			No Growth	X	NR	X	NR

NR= Not required per protocol

*Similar to PPQ, an average weight of (b) (4) will be used for calculations.

Test	Method No.	Acceptance Criteria	Timepoints (Months)				(b) (4)
			0 (Release)	1	3	6	
**Proposed specification based on data re-analyses requested by the FDA; final Specifications will be established after method re-validation							
***Visual Inspection is routinely performed as an (b) (4) test during manufacturing (b) (4). Per FDA request, visual appearance will be performed during stability to assess for the presence of aggregates or cell clumps in the DP and allow for homogenous test sampling. **Proposed specification based on data re-analyses requested by the FDA; final Specifications will be established after method re-validation.							
***Visual Inspection is routinely performed as an (b) (4) test during manufacturing (b) (4). Per FDA request, visual appearance will be performed during stability to assess for the presence of aggregates or cell clumps in the DP and allow for homogenous test sampling.							

Table 7. RP-L201 DP Long-Term Stability Data for Lot (b) (4) Bag, ≤-150°C)

Test	Method No.	AC	Timepoints (Months)	
			0 (Release)	(b) (4)
Mycoplasma	(b) (4)	No Mycoplasma Detected	No mycoplasma detected	No mycoplasma detected
Endotoxin		(b) (4)	(b) (4)	(b) (4)
Sterility ^a		No Growth	No Growth	No Growth
^a Sterility was tested by (b) (4).				

Table 8. RP-L201 DP Lots in Long-Term Stability Studies (≤-150°C)

(b) (4)	
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At the time of this BLA resubmission (Amendment 125806/0.82, received 26-Sep-2025), up to 3-month long-term stability data from (b) (4) DP lots, (b) (4), were submitted. Additional stability data (up to 6 months for Lot (b) (4) and up to (b) (4) months for Lot (b) (4) and sterility data (Lot (b) (4) at the (b) (4)-month timepoint were subsequently provided in Amendments 125806/0.87 (12-Nov-2025), 125806/0.103 (24-Feb-2026), and 125806/0.105 (25-Feb-2026). Corresponding BLA sections were updated in Amendments 125806/0.94 (22-Jan-2026) and 125806/0.105 (25-Feb-2026) in response to FDA's requests.

The Applicant initially proposed a 3-month DP shelf life when stored at $\leq -150^{\circ}\text{C}$. However, based on additional stability data available, the Applicant proposed extending the shelf life to **6 months**.

DP Stability Data

RP-L201 DP stability data for total viable cell count, cell viability, neutrophil adhesion, transduction efficiency, and (b) (4) are presented in **Figure 3** and **Figure 4**. The stability AC are depicted by red dotted lines.

Figure 3. RP-L201 DP Long-Term Stability Data (FDA generated)

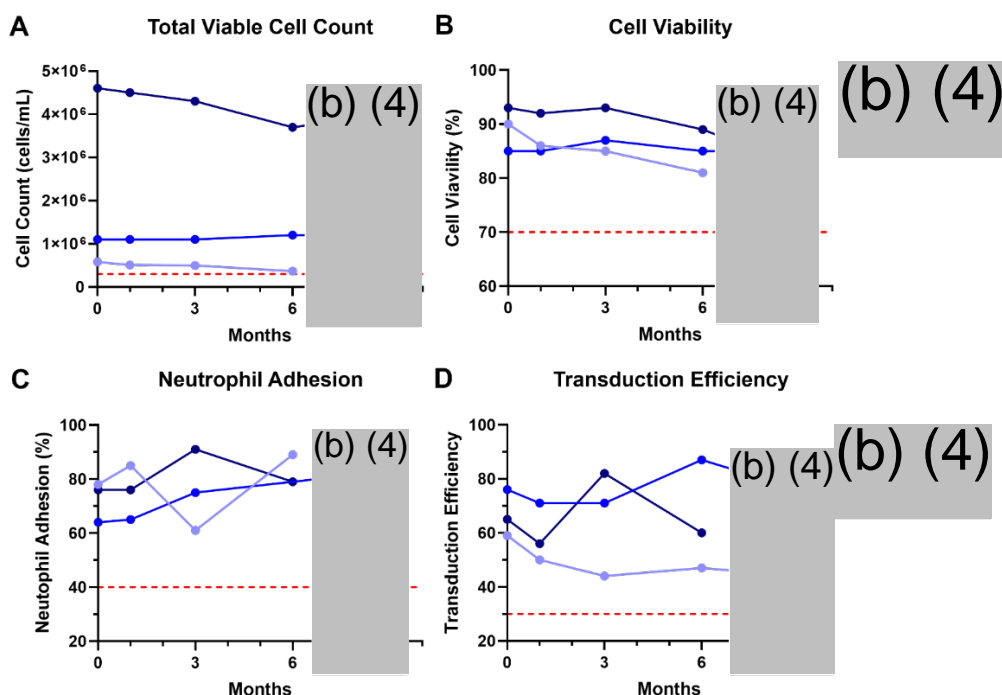
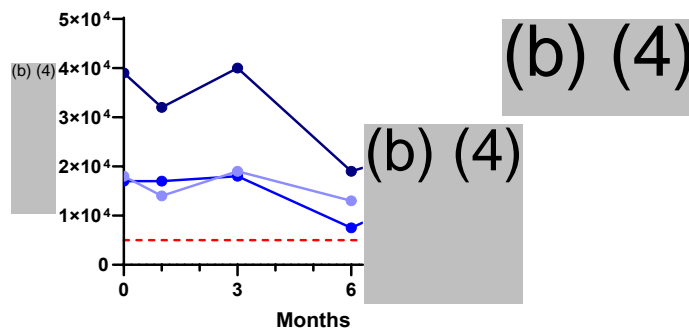


Figure 4. RP-L201 DP Long-Term Stability Data (b) (4) (FDA generated)



(b) (4) stability lots (b) (4) showed a downward trend in (b) (4) from the 3-month to the 6-month timepoint. In response to IR #9 issued on February 19, 2026, requesting that the Applicant explain this trend and justify the 6-month shelf life, the Applicant submitted additional stability data for DP lot (b) (4) at the (b) (4) month timepoint showing an increase in (b) (4) values between the 6- (b) (4) month timepoints in Amendment 125806/0.103 (24-Feb-2026). The Applicant explained that the decrease in (b) (4) values observed at 6 months is attributed to assay variability rather than an actual downward trend based on: (1) (b) (4) lots demonstrated an increase in (b) (4) values at the (b) (4) month timepoint, and (2) the intermediate precision of the (b) (4) assay is (b) (4) CV.

Reviewer Comment: The Applicant's explanation is acceptable.

In Amendment 125806/0.103, the Applicant also submitted negative sterility test results from (b) (4) lots packaged in (b) (4) bags at the 3-month timepoint. In Amendment 125806/0.105, the Applicant submitted additional negative sterility test results from (b) (4) in a (b) (4) bag at (b) (4) month time point. In the original BLA submission, the Applicant provided negative sterility test results from (b) (4) DP lots in (b) (4) bags; however, a (b) (4) method was used instead of a (b) (4) method per (b) (4). The DBSQC review identified that the (b) (4) method sensitivity was not adequately verified, and this method was deemed unacceptable during the original BLA review, see the DBSQC review memo for details on the (b) (4) sterility test method. In the current resubmission, the Applicant provided data to support suitability of the (b) (4) method, which was reviewed by DBSQC and deemed acceptable. The new (b) (4) method was used to assess sterility of current DP lots on the stability protocol. In general, to support a commercial shelf life, sterility data from at least (b) (4) DP lots in the final container closure at the end of shelf life should be provided. Although sterility data from (b) (4) in the final container closure at the (b) (4) month timepoint was provided, the Applicant also provided supporting sterility data from (b) (4) DP lots stored in (b) (4) bags at a 3-month time point and demonstrated container closure integrity of (b) (4) bag filled at the Applicant's developmental lab beyond (b) (4)-month time point. Considering the totality of supportive evidence provided, and that the bags are 510(K) cleared, the associated risk for sterility failure at 6-month time point is considered low, and the sterility data are

acceptable to support the proposed DP shelf life of 6 months. See the DMPQ review memo for further discussion regarding sterility assurance as part of the stability studies.

Post-Approval Stability Protocol

The stability acceptance criteria were revised based on communications through information requests to align with the revised DP release specification discussed in Section 3.2.2 of this review memo. The finalized post-approval stability protocol was submitted in Amendment 125806/0.105 (**Table 9**).

Table 9. Post-Approval Stability Protocol

Test	Method No.	Acceptance Criteria	Timepoints (Months)				(b) (4)
			0 (Release)	1	3	6	
Appearance	(b) (4)	<ul style="list-style-type: none"> • Color: colorless to white to red, including shades of pink, light yellow and brown suspension • Turbidity (Clarity): clear to slightly cloudy • Particulate: Free of intrinsic and extrinsic particulates. May contain small proteinaceous particles and visible cell aggregates (inherent particulates) 	X	X	X	X	(b) (4)
Total Viable Cell Count		3.4E+05 to 6.1E+06 cells/mL	X	X	X	X	
Cell Viability		(b) (4)	X	X	X	X	
(b) (4)			X	X	X	X	
CD34+ Cell Identity			X	X	X	X	
(b) (4)			X	X	X	X	
(b) (4)			X	X	X	X	
Transduction Efficiency			X	X	X	X	
Neutrophil Adhesion Assay			X	X	X	X	
Mycoplasma		No mycoplasma detected	X	NR	NR	NR	
Endotoxin		(b) (4)	X	NR	NR	NR	
Sterility		No Growth	X	NR	NR	NR	

NR= Not required per protocol

The Applicant commits to completing the ongoing stability studies and to placing at least one batch of healthy donor DP on stability annually at $\leq -150^{\circ}\text{C}$, provided that at least one batch is manufactured.

Reviewer Comment: The post-approval DP stability protocol and stability study plan are acceptable.

3.1.2.4 Reviewer Assessment

Based on the long-term stability data for up to (b) (4) month from (b) (4) DP lots and 6-month for (b) (4) in a scale-down container closure, sterility data from (b) (4) in a final container closure at a (b) (4) month timepoint, and the totality of supportive evidence provided, the FDA agreed with the proposed KRESLADI shelf life of **6 months at $\leq -150^{\circ}\text{C}$** . The shelf life of KRESLADI may be extended upon availability of additional stability data. Although, the Applicant did not perform any statistical analysis of the stability data, FDA review did not identify any concerning trends in the stability data, and all stability lots met the commercial AC at 6-month time point. Thus, a 6-month shelf life was provided as part of the CMC flexibility exerted during the review of this BLA.

3.1.3 Complete Response Item #3 – In-use Stability

Reviewed by SS

3.1.3.1 Text of CR item

Your application does not contain sufficient information demonstrating that the DP remains stable throughout the clinical preparation and administration process. Your in-use stability study included (b) (4) within the proposed cell concentration range, which exhibited a considerable decrease (b) (4) in (b) (4) by (b) (4) minutes post-thaw. Although administration of the DP during the clinical study occurred within this short timeline, the DP expiration after thaw could not be empirically determined due to insufficient data. Without a data-supported post-thaw expiry, we do not have adequate assurance that the DP maintains acceptable quality, safety, and efficacy throughout the clinical preparation and administration process. To support your label instruction, including the post-thaw expiration time, please provide in-use stability data from at least three DP lots across the range of proposed commercial cell concentrations. Additional studies to define thaw and DP handling conditions which allow a longer administration period would improve the administration process. The in-use stability data should demonstrate that DP critical quality attributes (e.g., sterility, potency, viability, etc.) are maintained under the condition described in the Package Insert. To ensure an adequate study design, please provide a draft validation protocol as an amendment to IND 18485 for review prior to initiating this study.

3.1.3.2 Overview of concern

During review of the original BLA submission, the Applicant did not provide sufficient information to determine an in-use hold time or to confirm product stability post-thaw. Multiple deficiencies were

identified in the in-use stability program. First, the only in-use stability data provided was CD34+ cell content (%), which does not demonstrate product stability. Second, additional data submitted during the review cycle showed significant decreases in live cell count (b) (4) minutes); however, the DP lots used were engineering lots (b) (4) with measurements (b) (4) the optimal detection range, and the study lacked product activity tests such as (b) (4) assays. Third, the new in-use stability study submitted in Amendment 125806/0.71 (May 31, 2024) used (b) (4) lot at (b) (4) cells/mL), which showed a (b) (4) decrease in (b) (4) by (b) (4) minutes post-thaw, making it difficult to support the Applicant's proposed 30-minute post-thaw stability claim. The in-use stability issues were communicated to the Applicant through Information Requests and teleconferences; however, they could not be adequately resolved during the original BLA review.

3.1.3.3 Firm's response to CR item

The in-use stability issue was originally identified as a deficiency in the CRL issued on June 14, 2024. However, following an informal teleconference with the Applicant on July 8, 2024, CBER OTP leadership reclassified this issue as an issue that could be resolved post-licensure with the experience from the clinical study used to define the initial commercial post-thaw hold time. Accordingly, this is no longer considered an issue that the Applicant must address in this resubmission. Refer to the teleconference minutes for further details regarding the discussion and decision.

In this resubmission, the Applicant provided only an updated in-use stability protocol and proposed to complete the in-use stability study as a post-marketing commitment (PMC #5). Based on in-use hold time data collected during the clinical study, the Applicant proposed a 30-minute in-use duration spanning from the initiation of KRESLADI thawing to the completion of infusion.

In response to FDA information requests (CMC IR #9, issued on 19-Feb-2026 and CMC IR #13, issued on 23-Mar-2026), the Applicant revised the test timepoints (Amendment 125806/0.103 received on 24-Feb-2026) and acceptance criteria (Amendment 125806/0.117 received on 24-Mar-2026). The final in-use stability protocol is outlined in **Table 10** below. In this study, (b) (4) healthy donor (HD) DP batches across the range of proposed commercial cell concentrations will be used, which were manufactured at the Rocket's Cranbury, NJ facility following the proposed commercial manufacturing process with slight modifications to the sampling process. Specifically, approximately (b) (4) of DP was manufactured according to the commercial process and 30 mL was filled into a (b) (4) bag and cryopreserved.

(b) (4) samples were filled into (b) (4) to serve as the control sample. Based on the process characterization studies, contact time of cells with DMSO is a critical process parameter that can impact cell count and viability of the DP. Consequently, trends observed during the in-use stability

study could result from DMSO contact time and rather than product interactions with the in-use materials. Therefore, these control samples will be held in (b) (4) at room temperature over the duration of the study and analyzed (total cell count, viability, (b) (4) and Neutrophil Adhesion Assay) to evaluate the potential impact of DMSO contact time. An additional (b) (4) were filled into (b) (4) and sent for release testing at (b) (4). The batch release data obtained for each of the batches that will be used in the in-use stability study are presented in **Table 11**.

Table 10. Summary of Proposed In-Use Stability Protocol

Test Name	Method	Acceptance Criteria	Post-Thaw	Post-Hold (T=0 minutes)	Infusion ^a	
					Collect ~5 mL (Beginning)	(b) (4)
Approximate Cumulative time (minutes) ^a			5	20	30	(b) (4)
Total Viable Cell Count ^b	(b) (4)	3.4E+05 – 6.1E+06 cells/mL	X	X	X	
Cell Viability		(b) (4)	X	X	X	
(b) (4)			X	X	X	
(b) (4)			X	X	X	
(b) (4) VCN			X	X	X	
(b) (4) VCN			X	X	X	
Neutrophil Adhesion Assay			X	X	X	
Endotoxin ^c		NR	NR	NR		
Sterility ^c	No Growth	NR	NR	NR		

^a Sampling points during infusion are based on volume. The time at the end of sampling will be recorded; however, cumulative time will be calculated from the (b) (4) assay. Collection of an (b) (4), provided that sufficient volume/cells are available.

^b If cell count is below the limit of detection, the sample will be (b) (4)

^c Will only be assessed on sample take at the end of collection.

NR: Not Required per Protocol

Table 11. Summary of Release Testing for DP In-use Stability Batches

Attribute	Acceptance Criteria	Batch			
Total Viable Cell count	(b) (4)	(b)	(4)	(b)	(4)
Cell Viability					
Neutrophil Adhesion Assay (b) (4)					
CD34+ Cell Identity					
(b) (4)					
(b) (4) VCN (b) (4)					
Transduction Efficiency (%TE)					
(b) (4) VCN					
Mycoplasma					
Endotoxin					
Sterility ^a	No Growth	No Growth	No Growth	No Growth	No Growth
^a Sterility tested per (b) (4).					

The materials to be used for the in-use stability study are summarized in **Table 12**.

Table 12. In-Use Stability Materials to be Evaluated

Material to be Evaluated	Manufacturer / Part Number	Justification
IV tubing w/Spike	(b) (4)	Material used at the US clinical site
30 ml syringe		Material used at the US clinical site
Stopcock		Material used at the US clinical site

3.1.3.4 Reviewer Assessment

The proposed in-use stability study plan is acceptable. As a regulatory flexibility, FDA will allow up to a 30-minute in-use duration at room temperature based on the hold time data obtained during the clinical study. This in-use condition is reflected in the United States Prescribing Information (USPI). A formal PMC communication was issued on 06-Mar-2026, and the Applicant has committed to performing the in-use stability study (PMC #5, Amendment 125806/0.115 received on 19-Mar-2026).

3.1.4 (b) (4)

Reviewed by AET

1 page determined to be not releasable: (b)(4)

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Reviewed by PKM

You did not demonstrate adequate suitability of the sterility test methods for your final drug product (DP). In amendment STN 125806/0.67, received on May 16, 2024, you agreed to perform the following:

(b) (4)

38

matrix to your product.

3.1.5.2 Overview of concern

In the original submission the Applicant proposed to use compendial method (b) (4) method for sterility. However, sterility method was not verified following (b) (4) guidelines as the (b) (4). Therefore, sterility of the DP cannot be assured. Furthermore, during the original review cycle, the Applicant proposed to use an alternative method (b) (4) for which product-specific validation was not performed by the Applicant. Therefore, (b) (4) assay validation was not sufficient to assure sterility of the DP. Sterility assay was reviewed by DBSQC. Refer to DBSQC review memo for additional information.

3.1.5.3 Firm's response to CR item

To address the CR letter item #5, the Applicant updated the sterility testing method from (b) (4) method and change the testing strategy for commercial release. For the DP sterility testing, the Applicant proposed testing (b) (4) of DP in (b) (4) method. For additional sterility assurance, the Applicant agreed to test (b) (4) method. Sterility testing of incoming leukapheresis material remained unchanged and will be performed using (b) (4) method. To implement these changes, the Applicant conducted additional method validation using (b) (4) representative lots of DP matrix. These studies demonstrated recovery of the (b) (4) challenge microorganisms and (b) (4) environmental isolates in the presence of (b) (4) of the RP-L201 DP material. All microorganisms including environmental isolates demonstrated recovery by day (b) (4). No Bacteriostasis and Fungistasis from the sample matrix was observed. The DP batches used to validate the (b) (4) were not manufactured at the commercial manufacturing facility. During the Type A meeting on December 10, 2024, the FDA asked the Applicant to provide additional data to demonstrate sterility assurance for the DP. In response to feedback provided to the Applicant during the Type A meeting, the Applicant manufactured (b) (4) prospective full-scale batches (b) (4) stability/sterility qualification batches and (b) (4) end of shelf-life batch) using the intended commercial process at the intended commercial facility (b) (4). These batches were tested at the intended commercial testing facility (b) (4). Results from these studies are presented in **Table 13**.

Table 13. Sterility data for DP and (b) (4) batches tested at release by (b) (4)

Batch number	Date of manufacture	Storage container	Sterility results (b) (4)	
			Drug Product	(b) (4)
(b) (4)	(b) (4)	(b) (4)	No growth	No growth
			No growth	No growth
			No growth	No growth
			No growth	No growth

3.1.5.4 Reviewer Assessment

Applicant's response to CR item #5 is acceptable. Sterility assay was reviewed by DBSQC. Refer to DBSQC review memo for additional information.

3.1.6 Complete Response Item #6 – DP potency assay validation

Reviewed by ALR

3.1.6.1 Text of CR item

Your DP potency assay method and validation report provided with the original BLA submission were not appropriately designed or controlled, which warranted a redesign of the assay and retrospective reanalysis of available validation data during the review cycle. However, due to the nature of the changes to the method, which impacts the way the data are visualized, (b) (4), analyzed, and interpreted, and the inability to retrieve the entire assay validation raw data set, a new validation study must be performed. Please conduct a prospective validation study for the revised DP potency assay method.

- a. To ensure an adequate study design, please provide a draft validation protocol as an amendment to IND 18485 for review prior to initiating this study and a timeline for study completion.*
- b. Since the specification for the potency assay will change from (b) (4), please propose a new acceptance criterion (AC) for the redesigned potency assay based on reanalysis of the clinical DP lots.*
- c. Please reanalyze your potency data from the process validation and comparability studies based on the new potency measurement.*

3.1.6.2 Overview of concern

The (b) (4) Assay using (b) (4) (Neutrophil adhesion assay) is performed to determine potency for KRESLADI lot release. During review of this assay at the IND phase and the original BLA submission, multiple issues were identified. Specifically, the main concerns were:

- 1) characterization of (b) (4) caused by the (b) (4)
- 2) assay readout based on (b) (4) changes from test articles compared to a (b) (4)
- 3) lack of appropriate assay and instrument standardization controls required for generating reliable (b) (4) measurements
- 4) multiple data and calculation errors identified in the validation report during review
- 5) discovery of missing raw validation data that was lost by the contract testing site (b) (4) and ultimately precluded the ability of the Applicant to perform a complete reanalysis of the original validation dataset in its entirety from an (b) (4) relative potency readout to a (b) (4) readout

At the request of FDA, the Applicant performed retrospective reanalysis of the available raw validation data, which showed that the assay, when assessed for (b) (4), could pass validation acceptance criteria (results reviewed previously and summarized in section 3.2.P.5.2 and 3.2.P.5.3 of the original CMC BLA review memo). However, due to the nature and breadth of the design and validation issues concerning this assay, a redesign and new prospective assay validation study was required. During the Type A meeting held with the Applicant on July 8, 2024, FDA agreed that the revalidation study could be performed as a PMC. In the current BLA resubmission, the Applicant has provided a draft revalidation protocol for FDA review and comment prior to initiating the new study.

3.1.6.3 Firm's response to CR item

In response to CR Letter Item 6a:

The Applicant provided a revised version of the validation report reviewed during the original submission, a draft protocol for a new prospective revalidation study, and a revised assay SOP. The documents are summarized in **Table 14**.

Table 14. Summary of new documents submitted to address CR letter item #6

Document ID	Document Title	Purpose
VR016188-ADD1.R02	Validation Addendum for the Determination of Drug Product Potency in Neutrophil Adhesion Assay	Revised validation addendum report. Includes a new Annex to report the results of the reanalysis based on (b) (4) (versus the original readout of (b) (4)). Also includes edits and corrections to errors identified during the BLA OS review. <i>Reviewer comment: The reanalyzed data were previously submitted under SN 0055. The results were reviewed at that time and summarized in section 3.2.P.5.2 and 3.2.P.5.3 of the original CMC BLA review memo. Therefore, this document will not be further reviewed in this memorandum.</i>
SPBT5544	Neutrophil Differentiation and Adhesion Assay by (b) (4)	Revised method SOP to update the analysis instructions such that (b) (4) is (b) (4) rather than (b) (4). Sample that was previously used as a reference standard will now be used as a positive control for system suitability. <i>Reviewer comment: An earlier draft SOP revision was provided under Amendment 125806/0.54 and was previously reviewed and summarized in section 3.2.P.5.2 and 3.2.P.5.3 of the original CMC BLA review memo. Clean and red-lined versions of the current revision were provided with this resubmission. The current SOP revision includes an additional change describing (b) (4). No additional changes were noted; therefore, this document will not be reviewed in further detail in this memorandum.</i>
VP016188-ADD2.V1.0	Neutrophil Differentiation and Adhesion Assay by (b) (4): Assay Validation Protocol	Draft protocol for prospective revalidation of the DP potency assay following the new analysis method.

The Applicant provided a draft protocol of the prospective revalidation of the KRESLADI potency assay for FDA review prior to initiating the new study. The proposed procedure for the new validation study mirrors the procedure followed for the original validation study, with the principal exception being the methodology used to analyze and report the data (i.e., assessment of (b) (4) as the assay (b) (4), rather than (b) (4) compared to a reference standard), as well as related modifications to system suitability and specificity criteria. **Table 15** provides a summary of changes between the original validation protocol and the draft validation protocol.

Reviewer comment: In CMC IR#7 (sent 04-Feb-2026), the Applicant was advised that the (b) (4) samples for the validation study should be prepared in a (b) (4) as those that were prepared for the CD34⁺ cell method validation. Specifically, (b) (4)

. In Response 3a,

(Amendment 125806/0.97, received 10-Feb-2026) the Applicant agreed to revise the validation protocol following FDA advice.

Table 15. Summary of changes to DP potency assay validation protocol

(b) (4)

(b) (4)

- The updated comparability study report provided with the current resubmission was reviewed (Module 3.2.P.2, Document 792219 v4.0) and confirms that the Applicant reanalyzed the potency data using the new (b) (4) method in place of the original (b) (4) increase approach, as requested. The updated statistical analyses continued to demonstrate equivalence between the (b) (4) manufacturing sites for potency across all analysis groups (pooled, healthy donor, and patient).
- The updated batch analysis provided with the current resubmission was reviewed (Module 3.2.P.5.4 Batch Analyses) and confirmed that the Applicant reanalyzed all batch data from clinical and healthy donor (PPQ, engineering, and stability) lots and reports the revised data as (b) (4).
- Based on the reanalyzed clinical lot potency data, the Applicant proposed an updated acceptance criterion of (b) (4) (Module 3.2.P.5.6 Justification of Specifications).

Reviewer comment: The revised comparability assessment did not alter comparability conclusions and continues to support the pooling of clinical data from both manufacturing sites. FDA agreed to the updated potency AC in CMC IR#5 Comment 1 (agreed through Amendment 125806/0.95, received 23-Jan-2026). The Applicant has adequately addressed CR Letter Items 6b and 6c.

3.1.6.4 Reviewer Assessment

The Applicant has performed all requested reanalysis of DP potency data; the results of updated analyses and revised AC are acceptable. Therefore, the Applicant has adequately addressed CR Letter Items 6b and 6c.

Regarding the revised draft revalidation protocol for the DP potency assay, the Applicant has agreed with FDA requests to update the preparation method for the validation samples and include (b) (4) in the study. The revalidation protocol (CR Letter Item 6a) is acceptable. The Applicant has committed to perform the DP potency assay revalidation study as a post-marketing commitment (captured under PMC #8).

3.1.7 Complete Response Item #7 – DP (b) (4) vector copy number (VCN) (b) (4) -VCN assays

Reviewed by ALR

3.1.7.1 Text of CR item

Regarding your (b) (4) vector copy number (VCN) (b) (4) -VCN DP release assays:

- a. Your (b) (4) -VCN assay was not adequately validated due to the use of validation samples that are not representative of the (b) (4) samples assessed during routine

performance of the assay. In Amendment STN 125806/0.53 (received April 17, 2024), you agreed to perform a validation addendum study to demonstrate the ability of the (b) (4) method to accurately detect and quantify LVV (b) (4) within a (b) (4) background, with anticipated study completion in December 2024. To ensure an adequate study design, please provide a draft validation protocol as an amendment to IND 18485 for input prior to initiating this study. Please provide the addendum validation report with your resubmission.

- b. You have not provided sufficient data to support the accuracy of the (b) (4)-VCN assay. Specifically, you have not adequately demonstrated that the number of (b) (4) (b) (4)-VCN analysis and subsequent Transduction Efficiency calculations are sufficient to ensure accurate and reproducible measurements of these outputs. Moreover, you have not provided empirical data to demonstrate how many (b) (4) are required to ensure sufficiently low run-to-run variability in your assay. The provided statistical justification is not adequate to ensure consistency between runs. Please conduct additional studies to evaluate accuracy and precision of (b) (4)-VCN and Transduction Efficiency when a range of (b) (4), including more than the current (b) (4), are (b) (4) to determine the acceptable number of evaluated (b) (4) to minimize assay variability.
- c. You do not standardize the amount of input (b) (4) for either of your VCN assays, therefore, each iteration of the assay will contain a variable amount of total (b) (4). Importantly, the quantity of total (b) (4) may impact the accuracy and precision of the assay. Please provide a robustness assessment evaluating (b) (4). This robustness assessment should utilize a (b) (4) VCN (b) (4)-VCN assays. You should also establish a system suitability control (SSC) to ensure that the total (b) (4) quantity in your VCN assays remains within a proven acceptable range.
- d. You have not designed the assay to ensure consistent performance. You have established an SSC for the (b) (4) based on general manufacturer's recommendations. Low input (b) (4), as represented by low (b) (4), may impair the ability to accurately measure VCN. Additionally, this SSC does not represent an (b) (4) value that would be expected from a given standardized input of (b) (4). In Amendment STN 125806/0.53 (received April 17, 2024), you agreed to refine the SSC for your assays and potentially implement a new SSC of (b) (4), however assay improvements have not been provided. Please provide refined SSCs with justifications based on historical data and appropriate statistical analyses with your resubmission.

3.1.7.2 Overview of concern

During the original submission (OS) review cycle, deficiencies in the validation of the (b) (4)-VCN assay used for DP release testing were identified. Specifically, in IR#5 (sent 26-Feb-2024), FDA noted that the validation samples consisted of (b) (4) background, which did not adequately represent the (b) (4) samples assessed during routine testing. In OS IR#9 (sent 04-Apr-2024), the Applicant agreed to perform a validation addendum study using a (b) (4). Additionally, through IR#12 (sent 23-Apr-2024), concerns were raised that the Applicant had not standardized (b) (4) input quantities for (b) (4) VCN or (b) (4)-VCN assays, which could impact assay accuracy and precision, and that the system suitability criterion (SSC) of (b) (4) was not representative of expected values from a standardized (b) (4) input. FDA also determined that the statistical justification provided for (b) (4)) was inadequate, as it relied on simulations and statistical modeling rather than empirical data demonstrating acceptable run-to-run variability. These concerns were communicated in CR Letter Item #7, which required: (a) validation addendum demonstrating accurate detection of (b) (4); (b) empirical studies evaluating accuracy and precision when varying numbers of (b) (4); (c) a robustness assessment of (b) (4) input quantity with establishment of appropriate SSCs; and (d) refined SSC for (b) (4) with statistical justification.

3.1.7.3 Firm’s response to CR item

Several new and updated documents were provided with the current resubmission and are summarized in **Table 16**.

Table 16. Summary of new documents submitted to address CR letter item #7

Document ID	Document Title	Purpose
SPBT5518 (Version 4)	(b) (4) for Vector Copy Number (VCN) Analysis	Revised method SOP for (b) (4) VCN (version 3 provided in SN 0001). Implements the commitment from original submission IR#4 (02-Feb-2024) to remove (b) (4). Minor typos were corrected. <i>Reviewer comment: The revisions are acceptable, and the document will not be further reviewed in detail in this memorandum.</i>
SPBT5519 (Version 5)	(b) (4) Assay with (b) (4) Analysis	Revised method SOP for (b) (4) assay (version 4 provided in SN 0001). Updated (b) (4) in response to FDA comments relayed in original submission IR#15 (28-May-2024), which stated that insufficient valid results were obtained in the validation study when (b) (4) were used. SSC updated to require both positive control and transduced test articles to show presence of both (b) (4). <i>Reviewer comment: FDA requested in original submission IR#12 (23-Apr-2024) that the Applicant update the method</i>


Document ID	Document Title	Purpose
		SOP to clearly state that (b) (4) is not acceptable. Applicant previously agreed in OS IR#12 Response 5a (Amendment 125806/0.58, submitted 30-Apr-2024) to revise this language to state that (b) (4)-VCN cannot be determined from (b) (4); however, the language was not updated. The Applicant was asked again to revise this language in resubmission IR#9 (sent 19-Feb-2026). The Applicant agreed to revise the SOP (Amendment 125806/0.103, submitted 24-Feb-2026) to ensure accurate and consistent information across documents.
SPBT5638 (Version 2)	Determination of Copy Number Variation in (b) (4)	Revised method SOP for (b) (4)-VCN (b) (4) (version 1 provided in SN 0001). Updated language to state that a (b) (4) should be used to perform (b) (4)-VCN assay (per discussion under original submission IR#12; 23-Apr-2024). Updated instrumentation information to remove references to the (b) (4) which was not validated (per discussion under original submission IR#4; 02-Feb-2024). <i>Reviewer comment: Language in (b) (4) SOP regarding minimum number of (b) (4) is acceptable and reflects what was previously discussed during review of the original submission; however, it is inconsistent with what is stated in SPBT5519. Additionally, per discussions under original submission IR#14 (Amendment 125806/0.66, submitted 15-May-2024), the positive (b) (4) threshold was updated from (b) (4); however, this threshold was not updated in this version of the (b) (4)-VCN (b) (4) SOP. The Applicant was asked to correct these discrepancies in resubmission IR#9 (sent 19-Feb-2026) and agreed to update all information appropriately (Amendment 125806/0.103, received 24-Feb-2026).</i>
VR301561.R01	Determination of Copy Number Variation in (b) (4) By (b) (4)	Revision of (b) (4)-VCN validation report provided in OS (SN 0001). A single typographical error was corrected to clarify APL sample ratios. <i>Reviewer comment: The revision is acceptable, and this document will not be discussed in further detail in this memorandum.</i>
VR301561-ADD1.v1.0	Robustness Report for Determination of Copy Number Variation in (b) (4)	Additional robustness testing performed to supplement (b) (4)-VCN (b) (4) method validation (VR301561.R01). <i>Reviewer comment: Additional robustness testing was not requested by FDA. In original submission IR#4 (02-Feb-2024), FDA requested clarification to explain missing robustness testing in the original validation report. The Applicant replied (Amendment 125806/0.38, received 09-Feb-2024) that robustness was conducted during development and reported in a separate study report (DR301561). FDA accepted this response during the OS review; however, the Applicant has elected to conduct additional robustness studies to support the commercial release assay. Study design and results are briefly summarized below.</i>

Document ID	Document Title	Purpose
VR016251.R01	Validation Report for (b) (4) Assay with (b) (4) Instrument Analysis	Revision of (b) (4) assay validation report provided in OS (SN 0007). Revisions were made to correct a number of data calculation and transcription errors discovered in the original report, which were identified after internal review by (b) (4). <i>Reviewer comment: The revisions were reviewed, and the corrected values have no impact on the results of the validation conclusions. Revisions to this report are not directly applicable to FDA concerns from CR Letter Item #7. Nevertheless, the corrections are acceptable, and this document will not be further reviewed in detail in this memorandum.</i>
VR016251-ADD1.R01	Validation Report Addendum for (b) (4) Assay with (b) (4) Instrument Analysis	Revision of (b) (4) assay validation addendum report provided in OS (SN 0001). Revisions were made to correct a number of typographical errors and to include reagent lot numbers that were not documented in the original report. <i>Reviewer comment: This report was reviewed in detail in the original submission CMC memorandum. No substantive revisions were made. This document will not be reviewed in further detail herein.</i>
VR016254-ADD1.R01	Validation addendum report for (b) (4) with Vector Copy Number (VCN) Analysis Endpoint	Revision of (b) (4) VCN validation report provided in OS (SN 0001). Added reagent/equipment tables. Addresses request for reagent/equipment tracking and other typographical errors noted in original submission IR#5 (sent 26-Feb-2024). <i>Reviewer comment: The corrections are acceptable, and this document will not be further reviewed in detail in this memorandum.</i>
n/a	(b) (4)-VCN Validation Protocol	Draft (b) (4)-VCN validation addendum protocol submitted for FDA review and comment prior to execution. <i>Reviewer comment: Submitted to address CR Letter Item 7a, and also designed to address concerns under Items 7c-d. Draft protocol is summarized below.</i>
1146569 v1.0	Development Report for VCN Determination Assay	Development report performed to ((b) (4)) <i>Reviewer comment: Submitted to support revalidation activities to address CR Letter Item 7a. Purpose and conclusions briefly described below.</i>
1410851 v1.0	Summary justification for (b) (4)-VCN sampling	Additional justification for (b) (4) for (b) (4)-VCN and transduction efficiency analysis using statistical modeling. <i>Reviewer comment: Submitted to address CR Letter Item 7b. See below for further details.</i>
1417688 v1.0	Evaluation of additional System Suitability Criteria for (b) (4) VCN and (b) (4)-VCN Assay	Development report describing preliminary evaluations of impact of (b) (4) quantity on VCN assay performance. <i>Reviewer comment: Submitted to partially address CR Letter Item 7c. Further reviewed below.</i>

In response to CR Letter Item #7a:

1 page determined to be not releasable: (b)(4)

(b) (4)



In response to CR Letter Item #7b:

During the original BLA review, FDA raised concerns regarding the adequacy of the statistical justification supporting the selection of (b) (4) for (b) (4)-VCN analysis and Transduction Efficiency calculations. The original submission included a statistical analysis based on (b) (4) confidence intervals from (b) (4) historical batches, which estimated that increasing from (b) (4) would improve confidence interval coverage from (b) (4) of batches meeting specifications. In original submission IR#12 (relayed April 23, 2024), we indicated that this statistical estimation was insufficient and requested empirical data demonstrating acceptable run-to-run consistency when (b) (4). Specifically, we requested that the Applicant conduct additional studies to evaluate accuracy and precision of (b) (4) VCN and Transduction Efficiency when a range of (b) (4) to determine the acceptable number of evaluated (b) (4) to minimize assay variability. The CRL reiterated this requirement, emphasizing that the provided statistical justification is not adequate to ensure consistency between runs and that empirical data, rather than statistical modeling, was necessary.

In the CRL response, the Applicant provided an updated statistical analysis (Document 1410851) using a more advanced (b) (4) approach with (b) (4) iterations comparing (b) (4) versus (b) (4), based on data from (b) (4) healthy donor batches manufactured during preclinical development. The analysis demonstrated that the mean (b) (4)-VCN and Transduction Efficiency values were nearly identical between the (b) (4) and (b) (4) simulations, with producer risk (falsely failing a passing batch) estimated at (b) (4) and patient risk (falsely passing a failing batch) estimated at (b) (4). Although the (b) (4) represents a more rigorous statistical evaluation than that provided in the original submission, it is a theoretical modeling exercise and the empirical experimental data that was requested were not provided.

Reviewer comments: Document 1410851 includes the same statistical simulation analysis, provided by a third-party statistician, that was previously provided under the first resubmission (Amendment 125807/0.078, submitted 01-Oct-2024), but has been updated to include additional discussion describing the (b) (4) approach. The FDA request for actual studies in which (b) (4) in (b) (4) runs to measure the observed run-to-run variability for (b) (4)-VCN and Transduction Efficiency, thereby empirically demonstrating the precision of these measurements, has not been addressed. Therefore, CR Letter Item #7b remains unresolved and must be addressed through PMC #9.

In response to CR Letter Items #7c and #7d:

During the original BLA review, FDA identified that the amount of (b) (4) for either the (b) (4) VCN or (b) (4)-VCN assays is not standardized, such that each iteration of the assay contains a variable amount of (b) (4). In original submission IR#12 (relayed April 23, 2024), FDA noted that the quantity of (b) (4) may impact the accuracy and precision of the (b) (4) assay and requested a robustness assessment utilizing a (b) (4) approach to evaluate allowable (b) (4) quantities. FDA further requested that the Applicant establish system suitability controls (SSCs) to ensure that total (b) (4) quantity remains within a proven acceptable range (CRL Item #7c). Additionally, FDA noted that the established SSC for the (b) (4) was based on general manufacturer recommendations and does not represent a value expected from standardized (b) (4) input. CRL Item #7d requested refined SSCs with justifications based on historical data and appropriate statistical analyses.

In the current resubmission, the Applicant submitted a development report (Document 1417688) providing a preliminary assessment of the impact of (b) (4) input quantity on assay performance and outlines a plan for SSC refinement. For the (b) (4) VCN assay, the Applicant conducted a proof-of-concept (b) (4) study evaluating (b) (4)

The results demonstrated that (b) (4) amounts from (b) (4) yielded acceptable precision across replicates (CV (b) (4)) and satisfied currently established SSC for (b) (4)

. Therefore, the results provided preliminary evidence that (b) (4) amounts within the (b) (4) range satisfy existing SSC and provide acceptable precision. The Applicant proposes to conduct additional studies using samples with VCN levels more representative of typical test samples (VCN (b) (4)) to establish the final (b) (4) and reassess SSC for this assay, including the number of (b) (4).

Reviewer comment: FDA requested the Applicant provide a timeline for study completion and submission of the final study report in IR#9. The Applicant responded (Amendment 125806/0.103, submitted 24-Feb-2026) that anticipated study initiation would occur by April 2026, study completion would occur by June 2026, and final report would be available by September 2026. These commitments are captured under PMC #11.

For the (b) (4)-VCN assay, the Applicant states that (b) (4) is not feasible because (b) (4)

Therefore, the Applicant proposes to maintain the current (b) (4) approach, which involves (b) (4)

Reviewer comment: The (b) (4) for each (b) (4) will remain (b) (4) in the assay procedure. This approach is acceptable given that (b) (4) quantification from (b) (4)


The Applicant further adds that SSC refinement for the (b) (4)-VCN assay, including the criterion for (b) (4), will be addressed during the validation addendum study through (b) (4) testing that challenges the low-end dynamic range for (b) (4) LVV (b) (4) (described in further detail under section CRL Item #7a).

Reviewer comment: FDA requested the Applicant explicitly include establishment of SSC as a validation objective for the new validation study in IR#9 (sent 19-Feb-2026), to which the Applicant agreed (Amendment 125806/0.103, submitted 24-Feb-2026). The commitment to refine (b) (4)-VCN SSC is captured under PMC #10.


Review of VR301561-ADD1.v1.0: Validation addendum report for (b) (4)-VCN (b) (4) assay robustness

(b) (4)

(b) (4)



(b) (4)






3.1.9 Complete Response Item #9 – DP cell count and viability (CCV) validation

Reviewed by ALR

3.1.9.1 *Text of CR item*

Regarding your cell count and viability validation studies:

a) (b) (4)



(b) (4)

- b) You indicated in Amendment STN 125806/0.34 (received January 25, 2024) that a backup (b) (4) had been purchased and was undergoing instrument and performance qualification. An assessment of the assay across instruments was not submitted to the BLA. Please perform additional validation activities to demonstrate intermediate precision of your cell count and viability assay using the new (b) (4) instrument and provide the addendum validation report with your resubmission.

3.1.9.2 Overview of concern

Deficiencies were noted during review of the cell count and viability method validation submitted with the BLA original submission. Specifically, robustness assessments were performed in the absence of baseline comparators (i.e., (b) (4)) and the impact of assay variables could not be appropriately evaluated. Additionally, the backup (b) (4) cell counter was not available at the time of assay validation; therefore, the study did not assess intermediate precision across all instruments that will be used to perform the commercial assay.

3.1.9.3 Firm's response to CR item

In the current resubmission, the Applicant provided one new report and two revised reports to support validation of the commercial CCV assay as summarized in **Table 20**.

Table 20. Summary of new documents submitted to address CR letter item #9

Report ID	Report Title	Purpose
VR016252-ADD2.v1.0	Assay Validation Report Addendum 2: Determination of Cell Count and Viability of Cryopreserved Cells	New validation addendum report describing supplemental robustness and intermediate precision evaluations to satisfy specific FDA concerns outlined in CR letter item #9.
VR016252.R01	Validation Report for the Determination of Cell Count and Viability	Validation report revision containing minor edits and typographical corrections. An earlier version of this report (VR016252.R00) was reviewed during the original BLA review to support late phase validation of the cell count aspect of the CCV method.
VR016252-ADD1.R01	Cell Count and Viability Determination using (b) (4)	Validation addendum report revision containing multiple edits, corrections, and clarifications to address FDA comments relayed to the Applicant during review of the original BLA submission (CMC IR#3 Comment 6, SN 0035). An earlier version of this report (VR016252-ADD1.R00) was reviewed with the original submission to

Report ID	Report Title	Purpose
		support late phase validation of the viability aspect of the CCV method.

Reviewer comment: The Applicant provided clean and redlined versions of report revisions VR016252.R01 and VR016252-ADD1.R01 with the current resubmission. As noted in the table above, previous versions of these reports were reviewed with the original BLA submission and were deemed acceptable to support validation of the commercial CCV assay. However, in BLA OS CMC IR#3 (sent 11-Jan-2024), FDA provided comments requesting a number of corrections and clarifications to address errors and inconsistencies that were found in these reports during review. The revised reports in the current resubmission were provided to address these comments. The updated reports were reviewed; the revisions are acceptable and will not be further described in detail in this memorandum.

Report VR01652-ADD2.v1.0 describes the results of an addendum validation study performed to assess robustness and intermediate precision. The previous evaluations reported in VR016252-ADD1.R00 were deficient due to lack of baseline/(b) (4) measurements for robustness comparisons and lack of inclusion of the backup instrument for intermediate precision, respectively. The results of the supplemental validation study are summarized in **Table 21**.

Table 21. Supplemental robustness and intermediate precision results for CCV method

(b) (4)

(b) (4)

(b) (4)

3.1.9.4 Reviewer Assessment

The Applicant completed additional intermediate precision and robustness assessments, as requested by FDA in CR Letter Item #9, and the results of the supplemental validation activities are acceptable. The commercial cell count and viability assay for KRESLADI release is sufficiently validated for licensure.

3.1.10 Additional Comment #15 - LVV Shelf Life

Reviewed by SS

3.1.10.1 Text of CR item

You proposed a shelf-life of (b) (4) for the LV-RP-L201 LVV based on up to (b) (4) stability data from LVV lots used for DP process performance qualification (PPQ) and (b) (4) supporting

stability data from LVV lots used for clinical DP manufacturing. However, you have provided only limited data for (b) (4). In your resubmission, please include any stability data collected prior to the resubmission date and re-analyze the LVV shelf-life per (b) (4)

3.1.10.2 Overview of Concern

During review of the original BLA submission, the Applicant proposed a shelf life of (b) (4) for LV-RP-L201 LVV when stored at (b) (4). However, multiple deficiencies were identified in the LVV stability program. (b) (4)

The LVV stability issues were communicated to the Applicant during the review cycle but could not be fully resolved.

3.1.10.3 Firm's Response to CR item

In this resubmission, the Applicant submitted additional LVV stability data and statistical analysis to support the proposed shelf life of (b) (4). The LV-RP-L201 lots used in the LVV stability studies and the LVV stability specification are presented in **Table 22** and **Table 23**, respectively.

Table 22. Summary of LV-RP-L201 (LVV) Batches on Stability

(b) (4)

(b) (4)

(b) (4)

3.1.10.4 Reviewer Assessment

Although statistical analyses for (b) (4) do not support an (b) (4) shelf life, and the Applicant provided limited justification, relying primarily on assay variability as an explanation, regulatory flexibility was applied to accept the LVV stability data in support of an (b) (4) shelf life for LV-RP-L201 when stored at (b) (4), based on the totality of up to (b) (4) stability data from (b) (4) LVV lots and consideration of assay variability.

3.2 Commercial release specifications

The commercial release specifications for the LV-RP-L201 LVV and KRESLADI were not finalized during review of the original BLA submission. In the CR letter conveyed on 14-Jun-2024, items #13

and #14 indicated that the acceptance criteria (AC) for the LVV and KRESLADI will be discussed once the application is otherwise acceptable.

During the review period for the BLA resubmission (Amendment 125806/0.82, received 26-Sep-2025), the commercial release specifications for the LVV and KRESLADI (agreed through Amendment 125806/0.95; received 23-Jan-2023) were arbitrated with Rocket. The final release specifications for the LVV and KRESLADI are shown below in **Table 25** and **Table 26** respectively. Please note that all AC are acceptable unless otherwise noted.

3.2.1 LVV Specification (Module 3.2.S.4.1)

Reviewed by AET

Table 25. Release specification for LV-RP-L201 LVV

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

3.2.2 DP Specification (Module 3.2.P.5.1)

Reviewed by ALR

Table 26 Release specification for KRESLADI

Attribute	Acceptance Criterion	# Lots	Justification
Appearance	<ul style="list-style-type: none"> Color: colorless to white to red, including shades of pink, light yellow and brown suspension Turbidity (Clarity): clear to slightly cloudy Particulate: Free of intrinsic and extrinsic particulates. May contain small proteinaceous particles and visible cell aggregates (inherent particulates) 	(b) (4)	<p>Color and turbidity AC based on observations made during appearance test validation of test samples representative of commercial DP concentrations.</p> <p>Particulate AC were proposed by FDA to more clearly define the types of particulates that are acceptable or unacceptable based on (b) (4)</p>
CD34 ⁺ Cell Identity	(b) (4)		Aligns with mean (b) (4) SD and the minimum %CD34 ⁺ from clinical experience. Proposed by FDA and agreed by Applicant.
(b) (4) VCN	(b) (4)		Two-sided limit represents the range of clinical experience (b) (4) SD. Proposed by FDA and agreed by Applicant.
(b) (4)-VCN	(b) (4)		Upper limit represents the highest observed value from clinical experience (b) (4) SD. Lower limit represents regulatory flexibility extended based on scientific rationale. Proposed by FDA and agreed by Applicant.
Transduction Efficiency	(b) (4)		One-sided limit based on the minimum clinical experience plus a small additional margin (b) (4) representing regulatory flexibility. Proposed by Applicant and agreed by FDA.

Attribute	Acceptance Criterion	# Lots	Justification
Neutrophil Adhesion Assay	(b) (4)	(b) (4)	One-sided limit representing the minimum clinical experience (b) (4) SD. Proposed by Applicant and agreed by FDA.
Total Viable Cell Count	(b) (4)		Range is representative of clinical experience and supported by stability data. Proposed by Applicant and agreed by FDA.
(b) (4)	(b) (4)		One-sided limit representing the minimum clinical experience. Proposed by FDA and agreed by Applicant.
Cell Viability	(b) (4)		One-sided limit representing the minimum clinical experience (b) (4) SD. Proposed by FDA and agreed by Applicant.
Endotoxin	(b) (4)		(b) (4) Proposed by Applicant and agreed by FDA.
Sterility	No Growth		Regulatory requirement. Proposed by Applicant and agreed by FDA.
Mycoplasma	No Mycoplasma Detected		Regulatory requirement. Proposed by Applicant and agreed by FDA.

Reviewer comment: FDA reviewed the Applicant's proposed DP specification provided in the resubmission (Amendment 125806/0.82, received 26-Sep-2025). In CMC IR#5 (sent 15-Jan-2026), FDA provided the Applicant with a revised DP specification. The Applicant agreed with the revisions and the DP specification was finalized through Amendment 125806/0.95, received 23-Jan-2026.

3.2.2.1 Appearance Testing

Reviewed by ALR

The specification for the investigational RP-L201 DP did not previously include appearance testing for DP release. The Applicant will implement an appearance test for the commercial KRESLADI DP that incorporates assessments of color, turbidity/clarity, and presence of particulates. The Applicant states that the method was developed based on (b) (4)

Reviewer comment: In response to CMC IR#5 (Amendment 125806/0.95; received 23-Jan-2026), the Sponsor clarified that the commercial appearance method is not (b) (4) as it employs a (b) (4)) than the (b) (4) required for the (b) (4) methods for color, clarity, and particulates. Additionally, the Applicant states that high concentration DP samples exhibit turbidity and color characteristics outside those described in relevant (b) (4)

*methods. Due to these differences, the Applicant stated that full validation was performed for the appearance method. The report (VR466022.V1.0) was provided with the IR response (Amendment 125806/0.95, received 23-Jan-2026) and results are summarized in **Table 28**.*

Table 27 summarizes the three versions of the appearance SOP that have governed the test over the lifecycle of this test method.

Table 27 Appearance test method versions reviewed in this submission

Document ID	Title	Changes from previous version	Reviewer Comments
C466022NRT.BSV	Non-Regulated Testing Method Document: Visual Appearance of the RP-L201 Drug Product	Original method document	<i>Applicant clarified in response to IR#5 (Amendment 125806/0.95, received 23-Jan-2026) that this version was designated “non-regulated” pending completion of method validation.</i>
SPBT7218 (Draft)	SOP: Visual Inspection of RP-L201 Drug Product	<ul style="list-style-type: none"> - (b) (4) - (b) (4) reference standard was removed from SSC 	<i>This SOP was referred to in the validation report as the guiding method SOP; however, the document was not provided in the submission. In response to IR#7 (Amendment 125806/0.97, 10-Feb-2026), the Applicant provided details of all differences between each method version, which are summarized in this table. The Applicant clarified that, although the (b) (4) reference was removed from this draft SOP version, the (b) (4) SSC evaluation was still performed in the validation and results were acceptable.</i>
SPBT7218	SOP: Appearance Test for the RP-L201 Drug Product	<ul style="list-style-type: none"> - Clarified that (b) (4) are prepared by (b) (4) - Updated reagents table to correctly include all (b) (4) color standards used (b) (4). Previous version only listed (b) (4). - Added (b) (4) reference back to list of SSC - Added details about OOS procedures 	<i>This is the final effective commercial appearance test method, which was provided under Amendment 125806/0.97 upon FDA request in IR#7 (sent 04-Feb-2026). In IR#7, FDA advised against using the terms “Visual Appearance” and “Visual Inspection” interchangeably. The Applicant agreed and updated the title of this document accordingly.</i>

Briefly, the appearance method is performed on a sample of final formulated DP that is collected (b) (4) DP bags. The lower (b) (4) volume was implemented in an effort to conserve total DP volume for patient administration. The sample for appearance is (b) (4)

(b) (4). The sample is evaluated in a (b) (4). The test article is compared to a (b) (4) and a series of commercially available reference standards for color and turbidity. The Applicant states that the sample must be essentially free of particulate matter and no detectable foreign matter should be observed.

Reviewer comment: In CMC IR#5 (sent 15-Jan-2026), FDA proposed an acceptance criterion that clearly states the DP should be free of intrinsic and extrinsic particulates but may contain inherent particulates. The terms “essentially” and “foreign matter” were removed. The Applicant agreed with FDA’s recommendation (Amendment 125806/0.95; received 23-Jan-2026).

The following assay suitability criteria must be met:

- (b) (4)
- Color: (b) (4)
- Clarity: (b) (4)

Assay Validation Report for Appearance Testing for the RP-L201 Drug Product (VR466022.V1.0)

(b) (4)

(b) (4)

(b) (4)

3.3 Review of clinical flow cytometry assay (Module 5.3.5.2.16)

Reviewed by AET

3.3.1 Background and Context

3.3.1.1 *Regulatory History*

A secondary efficacy surrogate endpoint in the RP-L201-0318 registrational study was frequency of patients who exhibited an increase in the percentage of CD18+ neutrophils to at least (b) (4) within 6 months of KRESLADI infusion. Concomitant with the increased expression of CD18, the Applicant also evaluated the levels of additional β 2 integrin subunits (i.e., CD11a and CD11b) on peripheral blood neutrophils. These clinical assessments were obtained with flow cytometry on peripheral blood (PB) or bone marrow (BM) samples at the Great Ormond Street Hospital (GOSH), UK.

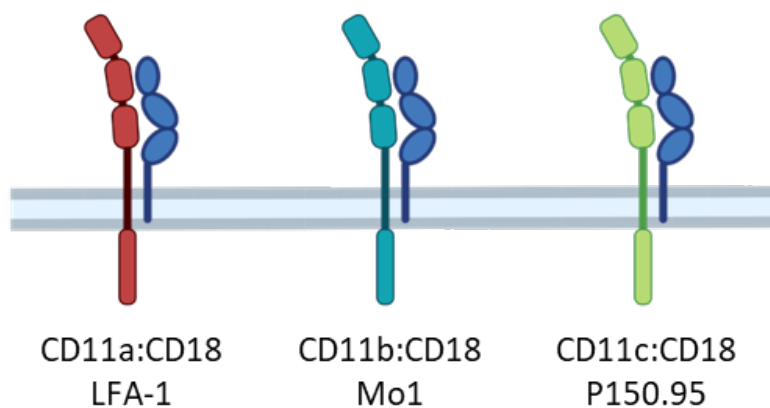
During the review of the resubmitted BLA, the clinical review team determined that an accelerated approval mechanism was the most likely approval pathway for this BLA given interpretability issues with the primary endpoints of the RP-L201-0318 clinical study. This accelerated approval will be based on sustained increases in CD18 (6p7) and CD11a expression on peripheral blood neutrophils in patients treated with KRESLADI. The decision to consider accelerated approval for this BLA submission was conveyed to the Applicant via an informal teleconference on 08-Jan-2026.

Because this assay will underpin the accelerated approval of KRESLADI, a comprehensive review of the CD11a assay, and a high-level review of the CD18 assay, was prepared as part of the review of the BLA resubmission and is detailed below.

3.3.1.2 Biological relevance of CD11a, CD11b, and CD18

Leukocyte adhesion disorder (LAD) is a rare primary immunodeficiency caused by the defective assembly of adhesion molecules required for white blood cell migration from blood vessels into tissues. LAD type 1 (LAD-1; the indicated condition for KRESLADI in BLA-125806) is caused by mutations in the *ITGB2* gene, which encodes the $\beta 2$ integrin subunit. The $\beta 2$ integrin subunit (also known as CD18) forms heterodimers with different CD11 moieties (CD11a, CD11b, and CD11c) to form functional, stable integrin complexes (see Figure 8).

Figure 8 – Integrin complexes using CD18 (Figure Generated by Reviewer)



Defects in the *ITGB2* gene lead to the loss of CD18, and the concomitant destabilization of CD11a:CD18 and CD11b:CD18 complexes, resulting in loss of surface expression of CD11a and CD11b. Importantly, certain rare mutations (~2% of all *ITGB2* mutations) produce CD18 molecules which retain surface expression but cannot form heterodimers with CD11a and CD11b. For this reason, quantitation of CD18+ cells alone has limited diagnostic and prognostic value (Levy-Mendelovich et al., *Immunology Research*, 2016). However, loss of CD18 surface expression due to *ITGB2* mutations results in loss of CD11a surface expression as well, supporting its use as a surrogate endpoint.


3.3.2 Analytical Procedure




3.3.2.1 *Narrative Description*


Flow cytometry assays for CD11a, CD11b, and CD18 are performed at the immunology laboratory at the Great Ormond Street Hospital (GOSH) according to SOP-778817. This SOP is executed as part of patient enrollment into the RP-L201-0318 clinical study, as well as the evaluation of treated patients to assess reconstitution of CD18 expression over time.



The analytical procedure involves the following steps:

(b) (4)




- | 
- | 
- | 



- | 
- | 

(b) (4)

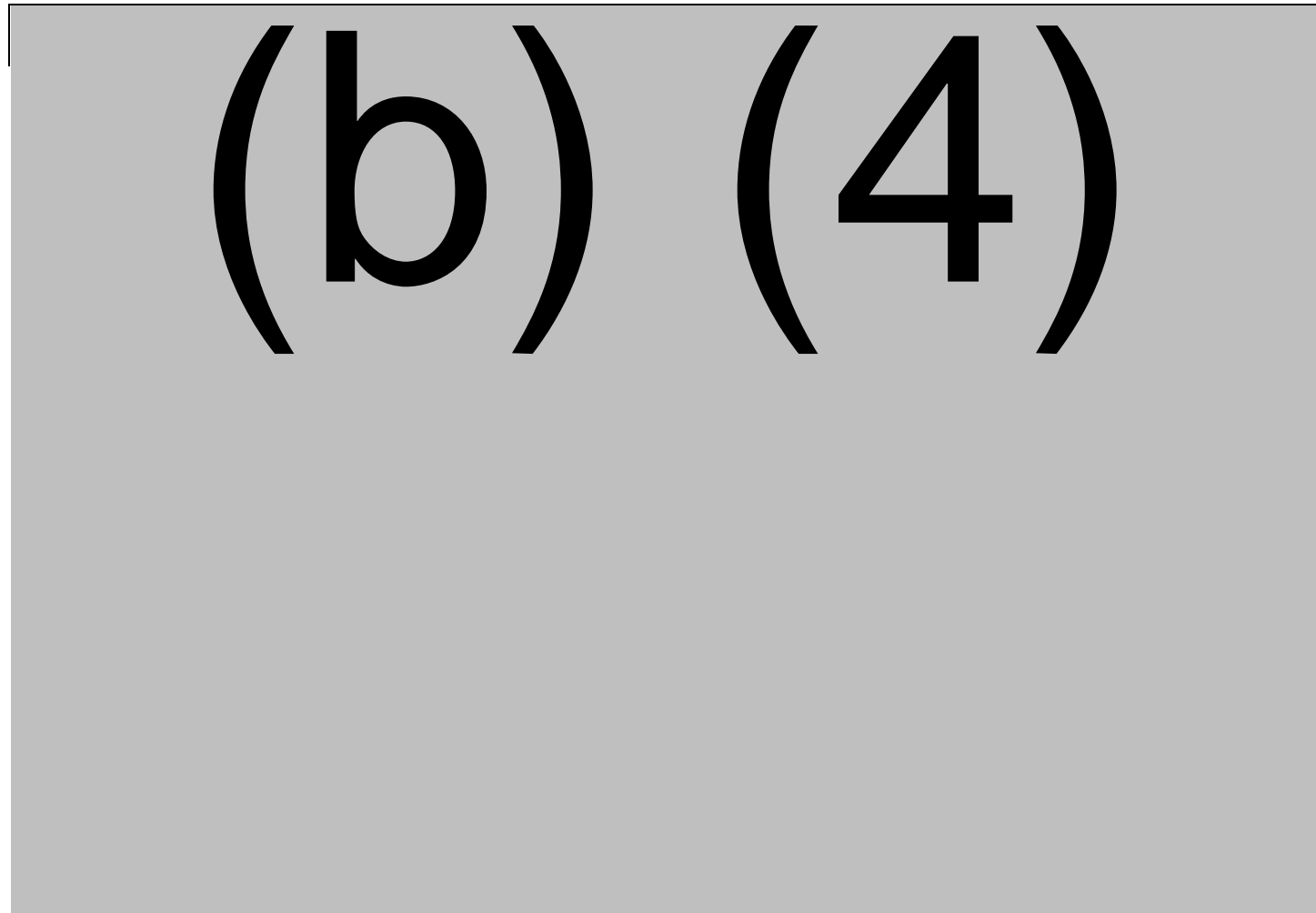
A large rectangular area of the document is redacted with a light gray background. The redaction covers approximately three lines of text.

3.3.2.2 Antibodies and flow panels used

Rocket uses ^{(b) (4)} distinct antibodies to execute the CD11a, CD11b, and CD18 clinical flow cytometry assays. The antibodies used are tabulated in **Table 29**, and the antibody staining panels are tabulated in **Table 30**.

Table 29. Fluorescent antibodies used in CD11a/CD11b/CD18 clinical assay

(b) (4)

The content of Table 29 is entirely redacted. A large gray rectangular box covers the table area, with the text "(b) (4)" centered in large black font.

(b) (4)

3.3.2.3 Gating Strategy

Rocket uses a (b) (4) gating strategy to select for (b) (4)

The gating strategy used in the clinical assay is summarized in **Table 31**.

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

3.3.2.4 *Quality control of flow cytometers*

GOSH employs several internal controls to ensure that the flow cytometers in the QC facility perform consistently from day-to-day. These internal controls include:

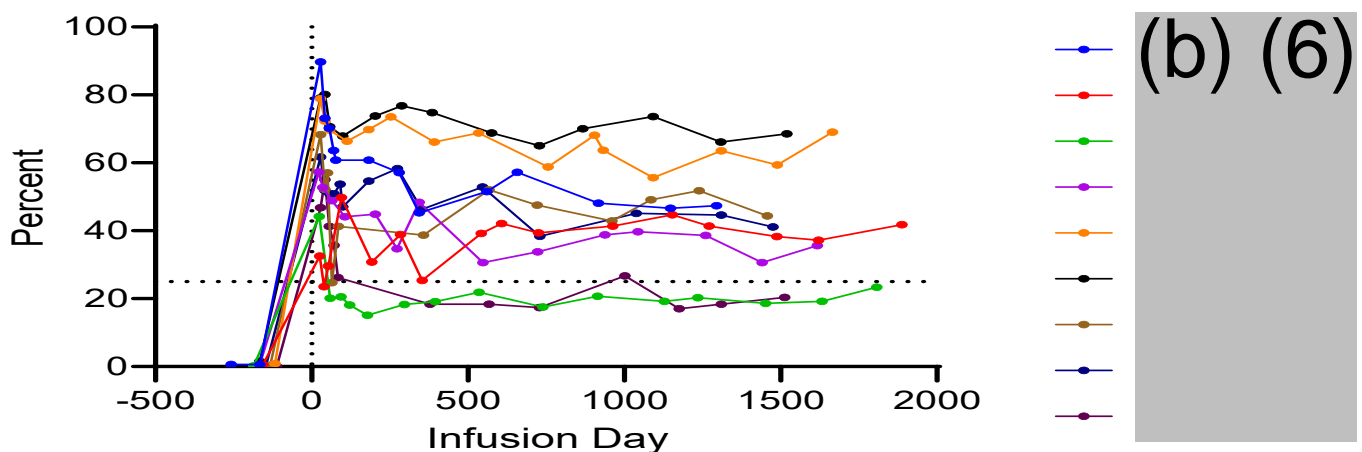
(b) (4)

(b) (4)

3.3.3.3 CD11a and CD18 clinical assay data

During the review cycle of the BLA resubmission, Rocket submitted updated clinical assay data for all patients treated on the RP-L201-0318 clinical study. The updated dataset indicates that patients have maintained steady-state frequencies of CD11a expression on neutrophils over time (see Figure 9).

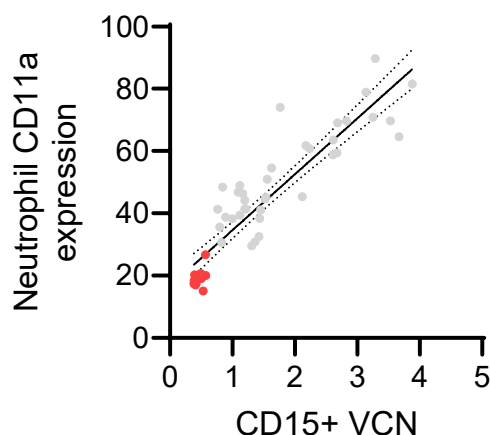
Figure 9 – CD11a and CD18 expression on neutrophils in patients treated with RP-L201
(Generated by Reviewer)



Of note, two patients ((b) (6)) have maintained steady-state CD11a frequencies below the empirically validated range of the assay ((b) (4)), shown as a horizontal dotted line).

Reviewer Comment – Two patients ((b) (6)) have exhibited stable CD11a surface expression at levels below the validated LoQ of the assay. The comparatively low CD11a frequency in these patients aligns with the results of other clinical assays (specifically VCN; see Figure), suggesting that these observations do not stem from poor sample quality or assay limitations.

Figure 10 – Correlation between PB neutrophil CD11a expression and PB neutrophil VCN (generated by reviewer)



Reviewer Comment – The frequency of CD11a+ neutrophils in peripheral blood is significantly correlated with the vector copy number of peripheral blood neutrophils over time ((b) (4)). Data from N=50 (same patients over time) assessments of PB VCN and CD11a frequencies are plotted, and an unconstrained linear regression was fitted to the data, along with ((b) (4)) confidence bands.

These data support that the comparatively low CD11a expression observed in patients ((b) (6)) stem from patient characteristics. The data points available from these patients are highlighted in red, which shows that these patients also exhibit low PB neutrophil vector copy numbers over time.

3.3.3.4 Conclusion regarding CD11a and subsequent follow up with Applicant

Based on the totality of data provided for the CD11a validation, it is the review team's conclusion that the lower limit of quantitation (LLOQ) is likely between a ((b) (4)) CD11a frequency, as opposed to definitively a ((b) (4)) CD11a frequency. However, while it is likely that the true LLOQ is between ((b) (4)) CD11a+, Rocket has only provided empirical data supporting a LLOQ of ((b) (4)).

CD11a+. If Rocket aims to expand the analytical range of the assay, Rocket should provide supplemental validation data evaluating assay performance at intermediate dilution levels.

During the review cycle for the complete response received on 26-Sep-2025, CMC conveyed an advice communication on 18-Feb-2026 which outlined the review team's conclusions regarding the validation status of the CD11a assay, in particular that the assay is validated with a LLOQ of (b) (4). The Applicant acknowledged this advice via email on 25-Feb-2026 and indicated that additional studies would be performed to expand the quantitative range of the assay.

3.3.3.5 Supplemental assay validations included in PMRs

On 24-Mar-2026, CMC and clinical leadership discussed the status of the CD18 assay validation and the resulting impact on the interpretability of the available clinical data, and the impact on the interpretability of the clinical data that would be generated in the confirmatory study. CMC conveyed that the CD18 assay is subjected to similar limitations as the CD11a assay; namely that the analytical range of the assay is restricted by the validation protocol itself (i.e., the relatively small number of dilutions queried) as well as the data provided (i.e., the unexplained abnormal results impacting precision and accuracy calculations).

To ensure that the confirmatory study generates robust results for CD11a and CD18 surface expression on neutrophils, CMC provided an additional post-marketing requirement (PMR) in which Rocket will provide the results from a supplemental validation performed over a wider analytical range to support the clinical study PMR that is required as part of an Accelerated Approval.

Reviewer Comment – In contrast to most CMC-related PMRs, this assay-related PMR is subjected to 21 CFR 601 subpart E regulations. This PMR will be provided in addition to the PMR related to the confirmatory clinical study that will be performed as part of accelerated approval. In essence, this PMR is being positioned as necessary to interpret clinical data, as opposed to a PMR related to the safety of the drug product.

3.4 Review of Package and Container labels (Module 1.14)

Reviewed by PKM

The package (cassette sticker) and the container labels (infusion bag sticker) were reviewed in conjunction with the APLB and the Office of Review Management and Regulatory Review (ORMRR). The Applicant submitted examples of package and container labels. The review of the labels identified several issues that were not in compliance with 21 CFR 610.62. The point size and typeface of the proper name on the package and container labels were not as prominent as the trade name. The submitted version contained intervening matter (shooting star) that adversely affected the prominence of the proper name. The package and container labels did not meet the 21 CFR 610.62(b) requirements of prominence and legibility. The submitted version of the labels did not contain the 2D barcode that contains, at a minimum, the appropriate NDC number (21CFR 201.25).

Additional instructional information was not included in the labels. A combined IR from CMC, APLB, and ORMRR was sent to the applicant on January 07, 2026, requesting the Applicant to make changes to the package and container labels to meet the 21 CFR 610.62 and 21CFR 201.25 requirements and submit an example of a lot information sheet. In response to the IR, the Applicant revised the package and container labels and provided lot information sheet (Amendment 125806/0.90, submitted 14-Jan-2026). Due to change in the AC of total viable cell counts, FDA asked the applicant to update the package and container labels with revised cell concentration and CD34+ cell concentration (communicated on 19-Mar-2026). In response, the applicant updated the package and container labels (Amendment 125806/0.116, submitted 23-Mar-2026). Updated version of package and container labels are shown in **Figure 11** and **Figure 12**)

Figure 11 KRESLADI Package label

Cassette Sticker (size 108x89mm)



marnetegrane autotemcel KRESLADI Suspension for IV infusion 30 mL containing $0.34 \text{ to } 6.1 \times 10^6$ cells/mL ($0.32 \text{ to } 6.1 \times 10^6$ CD34+ cells/mL)		NDC 83537-034-01  FPO 8353703401
FOR AUTOLOGOUS AND INTRAVENOUS USE ONLY.		Rx Only
Dosage: See Prescribing Information. See Lot Information Sheet for number of CD34+ cells per kg for this patient. Dose may be suspended in 1 or 2 infusion bag(s). Contents: Genetically modified autologous hematopoietic stem cells in a cryopreservative solution containing 5% DMSO. Store in vapor phase of liquid nitrogen ($\leq -150^\circ\text{C}$). Do not irradiate. Not evaluated for infectious substances. No Preservative. Do not use an in-line blood filter or infusion pump.		
Verify Patient ID First: FIRST NAME Last: LAST NAME DOB: DD-MMM-YYYY Rocket ID:		COI ID: DIN: XXXXXX XX XXXXXX XXX XXX XXXX XXXX LOT: XXXX-XXXXXX EXP: DD-MMM-YYYY Bag X of X
Manufactured for: Rocket Pharmaceuticals, Inc. Cranbury, NJ 08512 1-800-982-2410		U.S. Lic. # XXXX

Figure 12 KRESLADI container labels**Infusion Bag Sticker (40x48mm)**

Front	Back
<div><div>marnetegrane autotemcel</div><div>NDC 83537-034-01</div><div>KRESLADI</div><div>Suspension for IV infusion</div><div>30 mL containing 0.34 to 6.1×10^6 cells/mL (0.32 to 6.1×10^6 CD34+ cells/mL)</div><div>FOR AUTOLOGOUS AND INTRAVENOUS USE ONLY.</div><div>See Lot Information Sheet for number of CD34+ cells per kg for this patient.</div><div>Do not irradiate.</div><div>Do not use an in-line blood filter or infusion pump.</div><div><div><div>FPO</div><div>8353703401</div></div><div>Rx Only U.S. Lic. #XXXX</div></div></div>	<div><div>Verify Patient ID</div><div>First: FIRST NAME</div><div>Last: LAST NAME</div><div>DOB: DD-MMM-YYYY</div><div>Rocket ID:</div><div>COL ID:</div><div>DIN: XXXXXX XX XXXXXX XXX XXX XXXX XXXX</div><div>LOT: XXXX-XXXXXX</div><div>EXP: DD-MMM-YYYY</div><div>Bag X of X</div><div>Manufactured for: Rocket Pharmaceuticals, Inc. Cranbury, NJ 08512</div><div>U.S. Lic. #XXXX</div></div>

Reviewer comments: The revised version of package and container labels contain changes requested by the FDA that satisfy the expectations in 21 CFR 610.62 and reviewed by OGT. However, the Applicant neither included a 2-D barcode nor submitted an exemption request. ORMRR sent another IR (dated 18-Feb-2026) to the applicant requesting inclusion of a 2-D barcode in the labels or submission of an exemption request. In response to IR, the applicant submitted an exemption request (Amendment 125806/0.104, submitted on 25-Feb-2026) and provided a justification for not including a 2-D barcode. The applicant stated that the packaging labeling contains human readable product identifier and patient identification details. The packaging labeling and the proposed prescribing information all contain an instructional statement for the Healthcare Provider to verify the patient's identity and unique patient identification information printed on the packaging labeling. The applicant further stated that the contract manufacturing organization, (b) (4), is unable to print a 2-D barcode on the packaging labels for KRESLADI. The applicant requested the exemption be effective upon approval of BLA and until withdrawal of KRESLADI from sale. The exemption request was reviewed and granted by OCBQ. Please refer to APLB, ORMRR, and OCBQ review memo for additional information. The Applicant will update the labels with the US License number once it becomes available.