

CBER CMC BLA Review Memorandum

BLA STN 125746

Product Name

CARVYKTI
ciltacabtagene autoleucel

Reviewers

Maitreyi Chattopadhyay, Ph.D., OTAT/DCGT/GTB2
Tiffany Lucas, Ph.D., OTAT/DCGT/GTB2
Graeme Price, Ph.D., OTAT/DCGT/GTIB
Zhaohui Ye, Ph.D., OTAT/DCGT/GTIB

1. **BLA#:** STN 125746

2. **APPLICANT NAME AND LICENSE NUMBER**

Name:Janssen Biotech, Inc.

License Number:1864

3. **PRODUCT NAME/PRODUCT TYPE**

Proper Name/USAN: ciltacabtagene autoleucl

Proprietary Name: CARVYKTI

Company codename: JNJ-68284528

UNII Code: 0L1F17908Q

NDC Codes: 57894-111-01 (70 mL suspension in (b) (4) infusion bag); 57894-111-02 (30 mL suspension in (b) (4) infusion bag)

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

- a. **Pharmacological category:** BCMA-directed genetically modified autologous T cell immunotherapy
- b. **Dosage form:** Cell suspension for infusion
- c. **Strength/Potency:** A single dose contains 0.5 - 1.0×10⁶ viable CAR⁺ T cells/kg body weight up to a maximum of 1×10⁸ viable CAR⁺ T cells in either a 30 mL or 70 mL suspension in a patient-specific infusion bag
- d. **Route of administration:** Intravenous infusion
- e. **Indication:** For the treatment of adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody

5. **MAJOR MILESTONES**

Initial IND Submission (BB-IND 18080): May 28, 2018

Orphan Drug designation granted: February 1, 2019

Breakthrough Therapy Designation for JNJ-68284528: December 6, 2019

Pre-BLA type B Meeting: December 8, 2020

BLA Submission (Rolling BLA Module 3): March 31, 2021

First Committee Meeting: April 21, 2021

Filing Meeting: May 14, 2021

Mid-Cycle Meeting: July 15, 2021

Mid-Cycle Communication: July 29, 2021

Internal Late-Cycle Meeting: August 30, 2021

External Late-Cycle Meeting: September 20, 2021

PDUFA action due date (original): November 29, 2021

BLA 125746/0.57 designated as major amendment: October 21, 2021

PDUFA action due date: February 28, 2022

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Maitreyi Chattopadhyay, Ph.D. OTAT/DCGT/GTB2	Control of materials; (b) (4) DP stability; Adventitious agents safety evaluation
Tiffany Lucas, Ph.D. OTAT/DCGT/GTB2	3.2.S (b) (4) DRUG SUBSTANCE/Anti-BCMA CAR lentiviral vector
Graeme Price, Ph.D. OTAT/DCGT/GTIB	Cilta-cel specifications, analytical procedures, batch analyses, container closures, shipping validations
Zhaohui Ye, Ph.D. OTAT/DCGT/GTIB	Cilta-cel manufacturing process development & validation
Elena Gubina, Ph.D. OTAT/DCGT/GTB1	Consult review for (b) (4) Reagent
Steven Bauer, Ph.D. OTAT/DCGT/CTTB	Consult review for (b) (4) System
Sukhanya Jayachandra, Ph.D. OTAT/DCGT/CTB	Consult review for (b) (4) System
Elizabeth Lessey-Morillon, Ph.D. OTAT/DCGT/CTB	Consult review for (b) (4) medium
Thomas Finn, Ph.D. OTAT/DCGT/CTB	Consult review for (b) (4)
Zehra Tosun, Ph.D. OTAT/DCGT/TEB	Consult review for (b) (4) instrument
Alyssa Kitchel, Ph.D. OTAT/DCGT/TEB	Consult review for (b) (4) tubing set and buffer
Mercy Quagraine, Ph.D. OTAT/DCGT/CTB	Consult review for (b) (4) Preservation Media Solutions

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Yang Nan CDER/OPQ/ONDP/DNDP1	Consult review of DMF (b) (4) for lentiviral vector DS	Yes
The inter-center consult was assigned to the following offices: CDER/OPQ/OBP CDER/OPQ/ONDP	Consult review of DMF (b) (4) used in lentiviral vector manufacture	Cell culture media are not under ONDP's jurisdiction. OBP does not have experience in determining factors associated with toxicity for commercial CAR T cells. OBP provided relevant information from the DMF to the BLA review team.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
December 18, 2020	STN 125746/0.0	Initial submission (Unit 1 of 3) containing Modules 1,2,4,5
March 31, 2021	STN 125746/0.2	Unit 3 of 3 containing Module 3 and request for priority review

April 7, 2021	STN 125746/0.3	Request for Proprietary Name Review - CARVYKTI
April 30, 2021	STN 125746/0.5	Submission of 30-day late components including (b) (4) DP stability data, CoC/CoI validation
May 12, 2021	STN 125746/0.7	Response to IR#2 (Cassette and Infusion Bag Labels)
July 1, 2021	STN 125746/0.13	Response to IR #8 (CMC, part 1 of 2)
July 1, 2021	STN 125746/0.14	Updates and corrects to Module 3
July 6, 2021	STN 125746/0.15	Response to (b) (4) Records Request
July 7, 2021	STN 125746/0.16	Response to IR #8 (CMC, part 2 of 2)
July 16, 2021	STN 125746/0.17	Response to IR #11 (CMC, part 1 of 2)
July 23, 2021	STN 125746/0.18	Response to IR#12 (DBSQ, (b) (4))
July 23, 2021	STN 125746/0.19	Response to IR #11 (CMC, part 2 of 2, (b) (4) assay)
July 27, 2021	STN 125746/0.22	Response to IR #14 (CMC, (b) (4) assay)
July 30, 2021	STN 125746/0.27	Response to IR #10 (DMPQ, LVV (b) (4))
August 5, 2021	STN 125746/0.29	Response to IR #18 (CMC)
August 6, 2021	STN 125746/0.31	Additional information for to IR #18 response (CMC)
August 11, 2021	STN 125746/0.33	Response to IR #20 (CMC)
August 13, 2021	STN 125746/0.34	Updated infusion bag and cassette labels
August 23, 2021	STN 125746/0.36	Response to IR #23 (CMC)
August 27, 2021	STN 125746/0.37	Response to IR #25 (CMC, part 1 of 2)
August 31, 2021	STN 125746/0.41	Response to IR #24 ((b) (4) pre-inspection record request)
September 1, 2021	STN 125746/0.38	Response to IR #25 (CMC, part 2 of 2)
September 3, 2021	STN 125746/0.40	Response to IR #27 (CMC)
September 21, 2021	STN 125746/0.48	Response to IR #33 (CMC)
October 4, 2021	STN 125746/0.50	Response to IR #37 (DMPQ, shipping validation, (b) (4) cleaning validation)
October 14, 2021	STN 125746/0.56	Potency Assay ((b) (4)) validation and specification
October 14, 2021	STN 125746/0.57	Response to IR #41 (CMC)
October 20, 2021	STN 125746/0.58	Response to IR #45 (CMC)
November 2, 2021	STN 125746/0.66	Formal submission of materials for informal CMC meeting on 10/27/2021 (issues related to contract testing facility)
November 4, 2021	STN 125746/0.63	Redline documents for 125746/0.56
November 5, 2021	STN 125746/0.65	Response to IR #48 (CMC)
November 15, 2021	STN 125746/0.64	Response to IR #49 (CMC)
December 17, 2021	STN 125746/0.68	Updated infusion bag and cassette labels (NDC update in response to IR #49)
January 7, 2022	STN 125746/0.72	Response to IR#54 (CMC)
January 24, 2022	STN 125746/0.73	Response to IR#55 (CMC)
February 4, 2022	STN 125746/0.77	Response to IR# 58 (labeling comments)

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
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(b) (4)	(b) (4)	(b) (4)	Yes	Information provided is adequate to support the intended use. CMC Reviewer Sukhanya Jayachandra (CBER/OTAT/DCGT/CTB)
			Yes	Information provided is adequate to support the intended use. CMC Reviewer Steven Bauer (CBER/OTAT/DCGT/CTTB)
			Yes	No concerns with the reagent. CMC Reviewer Elizabeth Lessey-Morillon (CBER/OTAT/DCGT/CTB)
			Yes	No issues identified. CMC Reviewer Alyssa Kitchel (CBER/OTAT/DCGT/TEB)
			Yes	No issues identified. CMC Reviewer Alyssa Kitchel (CBER/OTAT/DCGT/TEB)
			Yes	No issues identified with the instrument. CMC Reviewer Zehra Tosun (CBER/OTAT/DCGT/TEB)
			Yes	Suitable for commercial manufacturing CMC Reviewer Elena Gubina (CBER/OTAT/DCGT/GTB1)
			Yes	No concerns with the reagent. CMC Reviewer Elizabeth Lessey-Morillon (CBER/OTAT/DCGT/CTB)
			Yes	Suitable for intended use. CMC Reviewer Tiffany Lucas (CBER/OTAT/DCGT/GTB2)
			Yes	Suitable for intended use. CMC Reviewer Tiffany Lucas (CBER/OTAT/DCGT/GTB2)
			Yes	No issues identified. CMC Reviewer Mercy Quagraine (CBER/OTAT/DCGT/CTB)
			Yes	Sufficient to support the BLA. CMC Reviewer Thomas Finn (CBER/OTAT/DCGT/CTB)
				Cell Manipulations Laboratory (Phase I/II)
	Trial Development and Support Laboratory	Yes	Not pertinent to the BLA review. Review not needed	
	Vector Production Facility	Yes	Not pertinent to the BLA review. Review not needed	
	(b) (4)	Yes	Licensed product. Review not needed	

(b) (4)		LVV and DP testing methods performed at (b) (4)	Yes	Type V MF: Additional information requested and reviewed CMC reviewer Tiffany Lucas (CBER/OTAT/DCGT/GTB2)
		(b) (4) Freezing Bags	Yes	510(k) cleared. Review not needed
		(b) (4)	Yes	Relevant sections reviewed by CMC reviewer Maitreyi Chattopadhyay (CBER/OTAT/DCGT/GTB2) No issues identified
		(b) (4)	Yes	The DMF does not contain sufficient information to support a BLA. Information pertinent to vector (b) (4) is provided in the BLA and is sufficient to support the BLA
IND 18080	Janssen	Clinical Trial of JNJ-68284528	N/A	Manufacturing process comparability reviewed and found acceptable during IND. CMC Reviewer Zhaohui Ye (CBER/OTAT/DCGT/GTIB)

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The CMC review team concludes that the manufacturing process, test methods and control measures for ciltacabtagene autoleucl (Cilta-cel; CARVYKTI) are capable of yielding autologous products with consistent quality attributes deemed acceptable for commercial manufacturing under BLA.

Cilta-cel is a genetically modified T cell immunotherapy product consisting of autologous T cells transduced with a lentiviral vector (LVV) expressing a chimeric antigen receptor (CAR) targeting the B-cell maturation antigen (BCMA). BCMA is expressed on the surface of normal and malignant plasma cells and plays a role in B cell survival. The CAR is comprised of two complementary (b) (4)-derived single domain antibodies (sdAbs) that bind to human BCMA, (b) (4) and the 4-1BB and CD3ζ chain T cell intracellular signaling domains. Binding of cilta-cel to BCMA-expressing target cells leads to signaling through the CD3ζ and 4-1BB domains, and subsequent CAR+ T cell activation. Antigen-specific activation of cilta-cel results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells. cilta-cel is indicated for the treatment of adult patients with multiple myeloma who have received at least four prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

Cilta-cel is formulated at 0.75 x10⁶ viable CAR+ T cells/kg (patients 100 kg or below) or 0.75x10⁸ viable CAR+ T cells (patients above 100 kg) and is cryopreserved at ≤ -120°C in cryopreservation media (b) (4). The formulated cell suspension is filled into (b) (4) (30 mL fill, when total viable cells formulated for the dose is less than or equal to (b) (4)) or (b) (4) (70 mL fill, when total viable cells is greater than (b) (4)) cryopreservation bags to maintain the final cell concentration within (b) (4) viable cells/mL. The clinically approvable commercial dose range will be 0.5 to 1x10⁶ CAR+ T cells/kg with a maximum of 1x10⁸ CAR+ T cells, provided as a single dose for infusion in one bag. The patient will receive

the entire quantity of product shipped to the administration site. Cilta-cel is shipped frozen in a vapor phase liquid nitrogen shipper. Following receipt at the administration site, cilta-cel is stored in vapor phase liquid nitrogen ($\leq -120^{\circ}\text{C}$) until the scheduled treatment time, when it is thawed and infused within 2.5 hours.

(b) (4)



Cilta-cel drug product (DP) is manufactured using patient apheresis material collected at qualified apheresis centers. (b) (4) at a local or centrally located (remote) (b) (4) center qualified by the applicant. The (b) (4) apheresis material is then shipped to the Janssen Pharmaceuticals manufacturing facility ((b) (4)) where it is inspected and stored until the initiation of DP manufacturing. The (b) (4) manufacturing process starts with apheresis (b) (4), which is followed by (b) (4) T cell enrichment in the (b) (4) system. The enriched cells are activated by (b) (4) and transduced by (b) (4) lentiviral vector in (b) (4). After (b) (4) of culture in (b) (4), the cells are harvested, (b) (4) and formulated in (b) (4). Final formulation calculation is performed at the step of (b) (4), based on patient weight and target dose using the in-process test results for (b) (4). Each dose is then filled into one appropriate size (b) (4) cryopreservation bag. Filled bags are examined for appearance, placed in individual metal cassettes, then cryopreserved using a (b) (4) and stored at $\leq -120^{\circ}\text{C}$ in vapor phase liquid nitrogen until lot release testing is complete. The DP bag required for administration is packaged into a vapor phase liquid nitrogen shipper and shipped to the administration site once patient administration has been scheduled. Cilta-cel stability at $\leq -120^{\circ}\text{C}$ in vapor phase liquid nitrogen was determined to be 9 months.

The cilta-cel control strategy begins with material qualification. Raw materials and reagents are accepted based on specified quality attributes. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents. Samples for in-process and lot release testing are collected at the appropriate stages in manufacture. Lot release test methods are suitably validated or verified, and product specifications are adequate to ensure product quality and consistency with DP used in the clinical study. The ability of the cilta-cel manufacturing process to consistently manufacture product that meets predetermined product specifications is demonstrated by process validation

studies. Chain of Identity/Chain of Custody (COI/COC) is established and validated at the collection site and maintained through the manufacturing process and administration.

B. RECOMMENDATION

I. APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product ciltacabtagene autoleucl (cilta-cel; CARVYKTI). The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics. This information satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products. Based on the information provided in the BLA submission and the information gathered during inspection of the Janssen Pharmaceuticals facility ((b) (4)) and record request review of Janssen Vaccines (b) (4) facility, the CMC review team recommends regular approval of this BLA.

II. COMPLETE RESPONSE (CR)

Not applicable

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Maitreyi Chattopadhyay, Ph.D. Biologist OTAT/DCGT/GTB2	Concur	
Tiffany Lucas, Ph.D. Biologist OTAT/DCGT/GTB2	Concur	
Graeme Price, Ph.D. Research Microbiologist OTAT/DCGT/GTIB	Concur	
Zhaohui Ye, Ph.D. Senior Staff Fellow Review Committee Chair OTAT/DCGT/GTIB	Concur	
Kimberly Schultz, Ph.D. Branch Chief OTAT/DCGT/DCGT/GTB2	Concur	
Denise Gavin, Ph.D. Branch Chief OTAT/DCGT/DCGT/GTB1	Concur	
Steven Oh, Ph.D. Deputy Director OTAT/DCGT	Concur	
Raj Puri, M.D. Ph.D. Director OTAT/DCGT	Concur	

Review of CTD

Table of Contents

3.2.S (b) (4) DRUG SUBSTANCE 13

 3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties..... 13

 3.2.S.2 Manufacture..... 13

 3.2.S.2.1 Manufacturer(s) 13

 3.2.S.2.2 Description of Manufacturing Process 14

 3.2.S.2.3 Control of Materials..... 18

 3.2.S.2.5 Process Validation and/or Evaluation 26

 3.2.S.2.6 Manufacturing Process Development 33

 3.2.S.3 Characterization 36

 3.2.S.3.1 Elucidation of Structure and Other Characteristics 36

 3.2.S.3.2 Impurities 42

 3.2.S.3.2 Controls of Critical Steps and Intermediates..... 37

 3.2.S.4 Control of Drug Substance 43

 3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)..... 43

 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures 48

 3.2.S.4.4 Batch Analyses 77

 3.2.S.5 Reference Standards or Materials 79

 3.2.S.6 Container Closure System..... 80

 3.2.S.7 Stability 82

 3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data..... 82

 3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment..... 84

3.2.S JNJ-68284528 DRUG SUBSTANCE..... 85

 3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties..... 85

 3.2.S.2 Manufacture..... 85

 3.2.S.2.1 Manufacturer(s) 85

 3.2.S.2.2 Description of Manufacturing Process 85

 3.2.S.2.3 Control of Materials 88

 3.2.S.2.4 Controls of Critical Steps and Intermediates..... 96

 3.2.S.2.5 Process Validation and/or Evaluation 106

 3.2.S.2.6 Manufacturing Process Development 117

 3.2.S.3 Characterization 130

 3.2.S.3.1 Elucidation of Structure and Other Characteristics 130

 3.2.S.3.2 Impurities 132

 3.2.S.4 Control of Drug Substance 136

 3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)..... 136

 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures 136

 3.2.S.4.4 Batch Analyses 136

 3.2.S.5 Reference Standards or Materials 136

 3.2.S.6 Container Closure System..... 136

 3.2.S.7 Stability 136

 3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data..... 136

 3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment..... 136

3.2.P DRUG PRODUCT 137

 3.2.P.1 Description and Composition of the Drug Product 137

 3.2.P.2 Pharmaceutical Development..... 138

 3.2.P.2.1 Components of the Drug Product 138

 3.2.P.2.2 Drug Product..... 138

3.2.P.2.3 Manufacturing Process Development 140

3.2.P.2.4 Container Closure System 140

3.2.P.2.5 Microbiological Attributes 142

3.2.P.2.6 Compatibility 142

3.2.P.3 Manufacture..... 143

 3.2.P.3.1 Manufacturer(s)..... 143

 3.2.P.3.2 Batch Formula..... 143

 3.2.P.3.3 Description of Manufacturing Process 143

 3.2.P.3.4 Controls of Critical Steps and Intermediates..... 143

 3.2.P.3.5 Process Validation and/or Evaluation 144

3.2.P.4 Control of Excipients..... 145

 3.2.P.4.1 Specifications..... 146

 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures 146

 3.2.P.4.4 Justification of Specifications 147

 3.2.P.4.5 Excipients of Human or Animal Origin 147

 3.2.P.4.6 Novel Excipients 147

3.2.P.5 Control of Drug Product..... 147

 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)..... 147

 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures 156

 3.2.P.5.4 Batch Analyses 180

 3.2.P.5.5 Characterization of Impurities 182

3.2.P.6 Reference Standards or Materials..... 183

3.2.P.7 Container Closure System..... 184

3.2.P.8 Stability 187

 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data..... 187

 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment..... 190

3.2.A APPENDICES 191

 3.2.A.1 Facilities and Equipment 191

 3.2.A.2 Adventitious Agents Safety Evaluation..... 191

 3.2.A.3 Novel Excipients..... 194

3.2.R Regional Information (USA) 194

Other eCTD Modules 196

 Module 1..... 196

 A. Environmental Assessment or Claim of Categorical Exclusion 196

 B. Labeling Review 196

 Full Prescribing Information (PI):..... 196

 Modules 4 and 5 198

 Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints 198

Table of Figures

Figure 1. (b) (4) Lentiviral Vector and CAR Design. BCMA Binding Domain ((b) (4)) are shown. 13

Figure 2. Representative Finished Lentiviral Vector Label (Amendment 37, received 08/27/2021) 18

Figure 3. Comparison of DP Lots Produced with LVV Manufactured at (b) (4) to Support Product Comparability..... 35

Figure 4. (b) (4) of LVV lots after (b) (4) 83

Figure 5. Clinical (b) (4) Apheresis Batches Across CPC Cites. 95

Figure 6. (b) (4) strategy for in process (b) (4) assay 100

Figure 7. Linear regression analysis of (b) (4) assays 128

Figure 8. Comparison of (b) (4) results 130

Figure 9. T cell differentiation status in cilta-cel DP lots 131

Figure 10. In Vitro Evaluation of cilta-cel DP Activity 132

Figure 11. Analysis of (b) (4) viability vs. clinical outcome 151

Figure 12. Analysis of (b) (4) per transduced cell vs. clinical outcome 153

Figure 13. Analysis of (b) (4) purity vs. clinical outcome 154

Figure 14. Analysis of CAR expression vs. clinical outcome 155

Figure 15. Analysis of (b) (4) vs. clinical outcome 155

Figure 16. Representative (b) (4) strategy for CAR T DP (b) (4) assay 170

Figure 17. Final product container closure: (b) (4) (left) and (b) (4) (right) cryostorage bags 185

Figure 18: Viability, %CAR and (b) (4) of DP developmental lots after long-term storage 188

Figure 19: Viability, %CAR and (b) (4) of PPQ and commercial lots after long term storage 189

Figure 20. Example of cilta-cel infusion bag label (70 mL suspension) 197

Table of Tables

Table 1. Manufacturing Sites, Locations, and Responsibilities for LVV Manufacturing and Testing 14

Table 2. Overview of Lentiviral Vector Manufacturing Process 15

Table 3. Raw materials not of Biological Origin in LVV Manufacture 19

Table 4: Raw Materials of Biological Origin in LVV manufacture 20

Table 5. Process Validation (PV) Results 26

Table 6. Stage (b) (4) In-Process Control and Process Parameter Results 27

Table 7. Stage (b) (4) Process Parameter Results 28

Table 8. Stage (b) (4) In-Process Control and Process Parameter Results 29

Table 9. Stage (b) (4) Process Parameter Results 29

Table 10. Stage (b) (4) Process Parameter Results 29

Table 11. Stage (b) (4) Process Parameter Results 30

Table 12. Stage (b) (4) Process Parameter Results 30

Table 13. Process Intermediate Hold Times and Temperatures 31

Table 14. Summary of Representative Shipping Validation Studies for Lentiviral Vector 31

Table 15. Manufacturing Changes Between Clinical and Commercial Lentiviral Vector (LVV) 33

Table 16. CPPs and PARs of Lentiviral Vector Manufacturing 38

Table 17. Early Downstream Bioprocessing and Proven Acceptance Ranges (Stages (b) (4)) 39

Table 18. Late Downstream Bioprocessing, Finishing Steps and PARs (Stages (b) (4)) 39

Table 19. IPCs With Acceptance Criteria for the Lentiviral Vector Manufacturing Process 40

Table 20. Janssen Proposed Lots Used to Establish Justification of Specifications 44

Table 21. Lentiviral Vector Lot Release Specifications 44

Table 22. Replication Competent Retrovirus Assay 52

Table 23. Replication Competent Lentivirus Platform Validation 53

Table 24. (b) (4) Assay Summary for Lentiviral Vector 55

Table 25. Validation for Lentiviral Vector (b) (4) Assay 57

Table 26. Scaled-Down Model Qualification to Support Use in (b) (4) Assay 61

Table 27. Platform Validation for (b) (4) 62

Table 28. Validation of (b) (4) Assay 64

Table 29. Verification of Appearance Particulates Assay 66

Table 30. Verification of (b) (4) Assay 67

Table 31. (b) (4) Validation of (b) (4) 68

Table 32. Platform Validation for (b) (4) 70

Table 33. Platform Validation of (b) (4) Assay for Lentiviral Vector Testing 72

Table 34. (b) (4) Validation 74

Table 35. Validation of (b) (4) Quantitation 76

Table 36. (b) (4) Lentiviral Vector ((b) (4)) Lots Provided in Batch Analysis.....78

Table 37. Batch Analysis Calculations to Support Commercial Lentiviral Vector Release78

Table 38. Reference Lot Lentiviral Vector Release Specifications and Results80

Table 39: (b) (4) Long-term Stability Plan82

Table 40: Long-term Stability Tests and Acceptance Criteria for LVV82

Table 41: Raw Materials NOT of Biological Origin in Cilta-cel manufacture89

Table 42: Raw Materials of Biological Origin in Cilta-cel manufacture89

Table 43. IPCs with predefined instructions for the cilta-cel manufacturing process.....97

Table 44 Summary of Analytical Procedures for In-Process Control Tests97

Table 45. Qualification acceptance criteria for in process (b) (4) assay99

Table 46. Linear ranges for in process (b) (4) assay marker detection99

Table 47. Stage (b) (4) nCPPs and CPPs101

Table 48. Stage (b) (4) nCPPs and CPPs101

Table 49. Stage (b) (4) nCPPs and CPPs102

Table 50. Stage (b) (4) nCPPs and CPPs103

Table 51. Stage (b) (4) nCPPs and CPPs104

Table 52. Cumulative Hold (b) (4) Study Design.....105

Table 53. Summary of (b) (4) Stage (b) (4) Process Validation Run Outcomes.....107

Table 54. IPC and CPP Result Summary from the Process Validation Runs.....108

Table 55. Comparison of Key Processing Differences between PV Batch (b) (4)109

Table 56. DP Release Testing Results – Process Validation Lots110

Table 57. Calculation table for organic extractables from high-risk polymeric materials.113

Table 58. Ciltacabtagene Autoleucl Production History Summary117

Table 59. A comparison of cilta-cel DP manufacturing processes.....117

Table 60. Summary of cilta-cel Manufacturing Process Comparability Studies.....119

Table 61. QTPP link to CQAs120

Table 62. Criticality Assessment Table for Quality Attributes121

Table 63. Criticality Table for Process Parameters.....123

Table 64. Historical DP release testing and specifications ((b) (4) and (b) (4)).....123

Table 65. Historical DP release testing and specifications ((b) (4)).....124

Table 66. Differences between clinical and PV/commercial (b) (4) assay method127

Table 67. DP Process Impurity Clearance.....133

Table 68. Composition and Concentration Ranges for 70 mL Drug Product in (b) (4) Bag.....137

Table 69. Composition and Concentration Ranges for 30 mL Drug Product in (b) (4) Bag.....137

Table 70. Summary of Clinical DP Batch Characteristics Data138

Table 71. Cryopreserved Drug Product Presentation139

Table 72. Organic Extractables and Leachables Results141

Table 73. (b) (4) release specifications146

Table 74. DMSO content (excipient) analytical procedure validation summary.....146

Table 75. Lot release and stability acceptance criteria for cryopreserved DP148

Table 76. Timing of sample acquisition, test sites, and SOPs149

Table 77. Maximum (b) (4) calculation152

Table 78. Observed data ranges and prediction intervals for DP purity154

Table 79. DP (b) (4) viability and cell concentration testing.....157

Table 80. Summary of acceptance criteria and validation results for cell count and viability analytical procedure.....158

Table 81. Results reporting for DP (b) (4) test.....160

Table 82. Summary of acceptance criteria and validation results for (b) (4) analytical procedure.....161

Table 83. (b) (4) assay validation summary167

Table 84. (b) (4) assay validation summary171

Table 85. Summary of acceptance criteria and validation results for (b) (4) analytical procedure..... 174

Table 86. (b) (4) assay validation summary 179

Table 87. Summary Clinical Lot Batch Analysis Data..... 181

Table 88. Batch analysis data from PV and commercial stability lots..... 182

Table 89. Description of final product container closure systems..... 184

Table 90: Test Parameters and Acceptance Criteria for Long-term Stability Studies..... 188

Table 91: Test parameters and acceptance criteria for in-use stability study 190

Table 92. Clinical CAR (b) (4) quantitation assay performance characteristics 201

Table 93. Clinical cytokine assay methods and validated ranges..... 202

Module 3

3.2.S (b) (4) DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

(b) (4)

[Redacted]

[Redacted]

(b) (4)

(b) (4)

[Redacted]

(b) (4)

[Redacted]

3.2.S JNJ-68284528 DRUG SUBSTANCE

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

Overall Reviewer’s Assessment of Sections 3.2.S.3.1 and 3.2.S.3.2

- ❑ The information and data provided were sufficient to support an appropriate characterization of the cilta-cel drug product.
- ❑ Impurity risk assessment for cilta-cel is acceptable
- ❑ The original submission did not contain sufficient details to evaluate T cell differentiation status and cilta-cel mode of action studies. This information was provided in Amendment 36 (received 08/23/2021) in response to IR#23 (08/10/2021).

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)

This information is reviewed in 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures

This information is review in 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.

3.2.S.4.4 Batch Analyses

This information is reviewed in 3.2.P.5.4 Batch Analyses.

3.2.S.5 Reference Standards or Materials

This information is reviewed in 3.2.P.6 Reference Standards or Materials.

3.2.S.6 Container Closure System

This Section reviewed by GEP

As the JNJ-68284528 DS proceeds directly to Cilta-Cel DP with (b) (4)

Note that the (b) (4) apheresis product (cellular starting material) is also stored in the (b) (4)

Please see Section 3.2.P.7 Container Closure System for details and reviewer’s assessment.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data

This information is reviewed in Sections 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data.

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

This information is reviewed in 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment.

3.2.P DRUG PRODUCT

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

Reviewed by ZY

The ciltacabtagene autoleucl drug product is an autologous cell suspension of transduced CAR positive (+) viable T cells formulated in a chemically defined freezing medium ((b) (4)) containing 5% DMSO.

The DP target dose for patients weighing 100.0 kg or below is 0.75×10^6 CAR+ viable T cells/kg patient weight with a specification range of $0.5 - 1.0 \times 10^6$ CAR+ viable T cells/kg. The target dose for patients weighing above 100.0 kg is 0.75×10^8 CAR+ viable T cells with a specification range of $0.5 - 1.0 \times 10^8$ CAR+ viable T cells. The DP is formulated for the target dose using a 70 mL fill volume in a single (b) (4) freezing bag, or a 30 mL fill volume in a single (b) (4) freezing bag. The DP bag is individually packed in an aluminum cryo cassette (b) (4). The cryopreserved drug product is stored at $\leq -120^\circ\text{C}$, in the vapor phase of liquid nitrogen.

The composition of the DP with 70 mL fill volume in (b) (4) bag is provided in Table 68. The composition of the DP with 30 mL fill volume in (b) (4) bag is provided in Table 69.

Table 68. Composition and Concentration Ranges for 70 mL Drug Product in (b) (4) Bag

Ingredient	Function	Amount per Bag		Concentration Specification
		CAR+ viable T Cells ^a	Total Viable Cells	Total Viable Cells/mL
ciltacabtagene autoleucl	Active	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Cryoprotectant (b) (4)	70 mL		NA

(b) (4)

[Redacted text block]

Table 69. Composition and Concentration Ranges for 30 mL Drug Product in (b) (4) Bag

Ingredient	Function	Amount per Bag		Concentration Specification
		CAR+ viable T Cells ^a	Total Viable Cells	Total Viable Cells/mL
ciltacabtagene autoleucl	Active	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Cryoprotectant (b) (4)	30 mL		NA

(b) (4)

[Redacted text block]

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

Reviewed by ZY

The cilta-cel manufacturing process is a (b) (4) process, (b) (4) and the DP formulation and fill. Cellular components and impurities of cilta-cel are reviewed in 3.2.S.3 Characterization.

The DP contains CAR+ viable T cells calculated based on patient weight, (b) (4), and formulated in (b) (4). The active component is comprised of (b) (4) T cells that have been transduced by a lentiviral vector encoding a CAR for BCMA. The T cell subset composition varies from subject-to-subject batch. The DP may also contain a small percentage of autologous NK (b) (4) cells. The characteristics of DP batches manufactured in the clinical studies are provided in Table 70.

Table 70. Summary of Clinical DP Batch Characteristics Data

	Average (n = (b) (4))	Minimum	Maximum
(b) (4) Viability	(b)	(b)	(4)
Phenotype (b) (4)			
Phenotype (% NK)			
Phenotype (b) (4) Purity)			
CAR Expression			

3.2.P.2.1.2 Excipients

(b) (4), the sole excipient in the DP, is a cryoprotectant that (b) (4) during cryopreservation to maintain (b) (4) viability and (b) (4). The specifications/compendial grade for the individual components of (b) (4) are provided in the BLA, but are limited to the level of detail that the supplier was willing to provide to Janssen. Additional information for (b) (4) is provided in BB-MF-(b) (4). Specifications for (b) (4) are provided in 3.2.P.4.1 Specifications.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Reviewed by ZY

Both the clinical and commercial cilta-cel DP are cryopreserved in (b) (4). The commercial DP presentation includes a 70 mL fill volume in a (b) (4) freezing bag or a 30 mL fill volume in a (b) (4) freezing bag. The total viable cell (b) (4) specification is between (b) (4) cells/mL with a target viable cell (b) (4) range between (b) (4) cells/mL, as shown in Table 71.

Table 71. Cryopreserved Drug Product Presentation

Attribute	Specification
Total Viable Cell Concentration	(b) (4) cells/mL in (b) (4)
Fill Volume/Primary Container	Release testing and Retains: (b) (4) Drug product: 30 mL fill volume in a (b) (4) freezing bag 70 mL fill volume in a (b) (4) freezing bag
Storage Condition	≤ -120°C in the vapor phase of liquid nitrogen for up to 9 months

History of Drug Product Formulation Development

A series of development studies using both healthy donor and patient derived materials were performed to determine the following:

- Stability of the DP with (b) (4) medium within the intended total cell concentration range ((b) (4) total viable cells/mL) at the recommended storage temperature as well as at an elevated temperature storage condition.
- Suitability of the 30 mL fill in (b) (4) bag as a scale-down model for the 70 mL fill in (b) (4) presentation to perform stability studies.
- Equivalence in product quality between the release testing container ((b) (4)) and the commercial DP presentations.
- Formulation robustness of DP manufactured from different lots of (b) (4).

(b) (4)



3.2.P.2.2.2 Overages

There are no overages included in cilta-cel.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties of cilta-cel DP are the same as that of the cilta-cel DS and are reviewed in 3.2.S.3.1 Elucidation of Structure and Other Characteristics.

3.2.P.2.3 Manufacturing Process Development

This information is reviewed in 3.2.S.2.6 Manufacturing Process Development.

3.2.P.2.4 Container Closure System

Reviewed by GEP

The primary container closure system ((b) (4) freezing bags) is described in detail in 3.2.P.7 Container Closure System. These bags are constructed from ethylene vinyl acetate and certified for use in accordance with (b) (4) Class (b)(4) and (b) (4) testing, for storage of blood cell products at liquid nitrogen vapor temperatures. The fluid path within the freezing bag is sterile and non-pyrogenic. Compatibility between the bags and DP was assessed by stability studies to monitor DP quality throughout the product shelf-life at recommended storage conditions ($\leq -120^{\circ}\text{C}$) as described in 3.2.P.8 Stability. Simulation studies to determine extractables and leachables from the primary container closure system were also performed based on FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, May 1999, and (b) (4)

These extractables and leachables findings are provided in study TV-TEC-165673 and are summarized below:

TV-TEC-165673: Extractables and leachables study

In this study, a simulation approach was taken for the assessment of extractables and leachables from the container closure system into the DP. This was required as the DP matrix ((b) (4)) would present analytical challenges. Therefore, (b) (4) bags were filled with model solvents ((b) (4)); extractables/leachables from labels were studied simultaneously to determine if there was any migration of ink or adhesive from printed labels into the DP. (b) (4) bags (with and without labels) were filled with (b)(4) mL of solvent and stored (b) (4). Sample extracts were then analyzed for (b) (4)

These readouts were selected to detect, identify, and quantitate the broadest range of organic compounds and elemental impurities.

The top (b)(4) organic extractables and leachables detected are shown in Table 72, which also indicates the potential patient exposure to these compounds and their safety impact. Safety assessments were based on a worst-case exposure to (b)(4) bags of product (normally only one bag would be used), the surface area of the (b) (4) bag ((b) (4)), and potential for repeat dosing (normal dosing is expected to be 1 bag over a patient lifetime, but a repeat dose at least one month apart may be needed in some cases). Acceptable intake (maximum exposure to patient) for any individual impurity was assessed as (b)(4) per day for a treatment duration (b) (4) per (b) (4) guidelines.

Table 72. Organic Extractables and Leachables Results

Extractable/ leachable	CAS #	Bag configuration	Max quantity (µg/cm ²)	Max. exposure to patient (µg/dose)	PDE (µg/day)	Safety margin	Safety concern
<div style="font-size: 48px; font-weight: bold;">(b) (4)</div>							No
							No
							No
							No
							No
							No
							No
							No
							No
							No

Abbreviations: CAS # - Chemical abstracts service number; PDE – Permissible daily exposure; NA – not available

Acceptable intake (maximum exposure to patient) for any individual impurity was assessed as (b) (4) per day for a treatment duration (b) (4) per (b) (4) guidelines for mutagenic compounds. Only (b) (4) organic compounds (b) (4) exceeded this level and were individually assessed. The parenteral tolerable intake level of (b) (4) is (b) (4), so for a 70 kg individual the permissible daily exposure would be $(b) (4) \times 70 = (b) (4)$ (resulting in a safety margin of (b) (4)). For (b) (4), the parenteral tolerable intake level is (b) (4), resulting in a permissible daily exposure for a 70 kg individual of $(b) (4) \times 70 = (b) (4)$ and a safety margin of (b) (4). Based on these assessments, none of the detected organic compounds pose a safety concern at the levels detected based on the worst-case scenarios of DP storage conditions and dosing regimen. There were no measurable differences between samples from bags with and without printed adhesive labels.

No inorganic elements were detected above the limit of detection ((b) (4)) by (b) (4), with only trace amounts of (b) (4) reportable in (b) (4). Therefore, the risk of elemental extractables and leachables is minimal.

Reviewer comment: *The conclusions of the extractables and leachables study indicate no risk to patients from organic or inorganic compounds at the levels detected. While the study was performed using (b) (4) bags, the results are applicable to the smaller (b) (4) bags which are manufactured of the same materials and stored similarly. Note that the solvent extraction volumes used ((b) (4) mL in a (b) (4) bag) are smaller than the DP fill volume (70 mL) and the extraction conditions are harsher (b) (4) (b) (4)) than would be used for commercial product (stored at (b) (4), where mass transfer between the bag and the enclosed solution would be essentially halted). The study combination of the smaller extraction volume and higher temperature would be expected to result in higher concentrations of extractables and leachables than would be seen in the commercial DP. There are no extractables or leachables concerns.*

3.2.P.2.5 Microbiological Attributes

Reviewed by GEP

Protection of finished DP from microbial contamination during storage, shipping, and administration is provided by the container closure system ((b) (4) EVA freezing bags, described in 3.2.P.7 Container Closure System). While DP sterility is tested at release and during stability assessments, additional container closure integrity testing (CCIT) was performed to show consistent integrity of these bags and their ability to provide a barrier to microbial contamination of the DP. CCIT used the (b) (4) test method on cryobag samples filled with (b) (4) (70 mL fill for (b) (4) bags and 30 mL fill for (b) (4) bags). In this method, the bags are (b) (4)

A threshold limit for test positivity ((b) (4)) was defined by (b) (4). Negative control bags filled with (b) (4) that have no known defect are used to control for (b) (4) in the test apparatus that might lead to false positive results.

(b) (4) rounds of CCIT were performed. For ease of review container closure integrity after manufacturing at the (b) (4) site is presented below; container closure integrity after shipping is presented in 3.2.P.3.5 Process Validation and/or Evaluation - DP shipping qualification. For the post-manufacturing CCIT, (b) (4) freezing bags with a 30 mL fill of (b) (4) were used. Janssen considers the (b) (4) bags representative of both DP formats as bag sealing and integrity are independent of the product, fill volume, or DP bag size. In addition, the (b) (4) bags use identical materials, the same fill tube and tube placement, and follow the same sealing, fill tube cutting, visual inspection and freeze process. For the (b) (4) bags, (b) (4) independent fill runs were performed at (b) (4) on different days, with (b) (4) bags filled in each run. CCIT was performed for all (b) (4) bags with no leaks detected. These results confirm the integrity of the (b) (4) bags used as the DP container closure system after filling using the commercial fill-finish procedure and equipment.

Reviewer comment: Note that the (b) (4) bag fill runs are much larger than DP manufacturing runs (where typically (b) (4) DP bags will be filled). While Janssen is correct that the (b) (4) bags are similar, they differ in surface area and seam length (the (b) (4) bags are larger in all dimensions), which increases the number of potential failure points in the (b) (4) bags. In Amendment 36 (response to CMC IR of 08/10/2021, received 08/23/2021), Janssen clarified that post-manufacture CCIT was intended to demonstrate the effectiveness of the bag sealing process which is identical for (b) (4) and (b) (4) bags. Janssen maintains that as each bag is (b) (4) tested by the manufacturer, inspected on receipt, examined during filling, and inspected prior to cryopreservation, any breach in seam would be detected and the bag rejected for use. This response is reasonable. There are no concerns with container closure integrity in terms of protection from microbial ingress.

3.2.P.2.6 Compatibility

Reviewed by ZY

In-use stability and compatibility studies were performed at both low ((b) (4) viable cells/mL) and high ((b) (4) viable cells/mL) cell concentrations. Compatibility was assessed using (b) (4) commercially available DP infusion sets made from different polymeric materials. Infusion sets either with single or dual spikes (for connecting DP/ saline bags) and either with or without a non-leukocyte depleting in-line filter were tested. A total of (b) (4) conditions were tested.

All DP bags were thawed using a 37°C water bath and subjected to visual inspection. The thawed DP was held in the DP bag for 2.5 hours and administered via gravity over 1 hour under ambient temperature and (b) (4) conditions. (b) (4)

(b) (4)

To determine in-use stability, viability, viable cell concentration, (b) (4), CAR expression and cytotoxicity (b) (4) were evaluated at 3 pre-infusion timepoints (T = 0, T = 1.5 h, and T = 2.5 h) and at 1 post-infusion timepoint (T = (b) (4)) in each condition.

The post-infusion DP (b) (4) met the (b) (4) acceptance criteria ((b) (4)) for all (b) (4) study conditions with an average of (b) (4). Test results also met acceptance criteria for (b) (4) - infusion samples for all (b) (4) study conditions and for all assays, with the exception of (b) (4) (out of (b) (4) total: (b) (4) conditions x (b) (4) time points) test results not reported due to invalid assays. Overall, these study results demonstrated that DP retained its biological quality attributes throughout the tested preparation, hold and administration (the proposed after thaw hold time at clinical sites is ≤ 2.5h; post-thaw stability is also reviewed in 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data) steps regardless of DP fill volume, DP cell concentration, infusion set, presence or absence of an in-line filter and the flush method.

Overall Reviewer’s Assessment of Section 3.2.P.2:

Together with the manufacturing process development information provided in 3.2.S JNJ-68284528 DRUG SUBSTANCE, pharmaceutical development of cilta-cel is adequately described. Development studies demonstrate the DP formulation robustness and the suitability of the 30 mL fill as a scale-down model for the 70 mL fill in stability studies. Equivalence in product quality between the release testing (b) (4) and commercial DP presentations is shown. DP container closure integrity test, and the extractables and leachables study were acceptable. In-use stability and cilta-cel compatibility with commonly used infusion sets were demonstrated.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

This information is reviewed in 3.2.S.2.1 Manufacturer(s).

3.2.P.3.2 Batch Formula

Reviewed by ZY

The batch formula for the DP with 70 mL fill volume in (b) (4) bag is presented in Table 68. The batch formula for the DP with 30 mL fill volume in (b) (4) is presented in Table 69.

The targeted amounts indicated in batch formula tables are calculated for a batch size of one patient dose (1 bag). If a sufficient number of cells are produced, additional bags may be manufactured in a batch. However, the total number of DP bags manufactured per batch must not exceed the total number of bags simulated during the aseptic process simulation ((b) (4) bags).

Overall Reviewer’s Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

- Manufacturer information is provided in 3.2.S.2.1 Manufacturer(s).
- Cilta-cel batch formula is adequately described

3.2.P.3.3 Description of Manufacturing Process

This information is reviewed in 3.2.S.2.2 Description of Manufacturing Process.

3.2.P.3.4 Controls of Critical Steps and Intermediates

This information is reviewed in 3.2.S.2.4 Controls of Critical Steps and Intermediates.

3.2.P.3.5 Process Validation and/or Evaluation

Reviewed by GEP

Manufacturing process validation is described in 3.2.S.2.5 Process Validation and/or Evaluation. Additional information presented in 3.2.P.3.5 Process Validation and/or Evaluation (and not reviewed elsewhere) describes DP shipping qualification.

DP shipping qualification

DP is shipped from Janssen ((b) (4)) using a passive shipping system ((b) (4) dry vapor cryoshipper, described in detail in 3.2.P.7 Container Closure System) which provides thermal and physical protection for frozen DP filled into the container closure system. This passive shipping system was qualified through laboratory testing to demonstrate that the specified temperature of ((b) (4)) is maintained within the shipper. This qualification study used shippers containing the maximum payload ((b) (4) bags containing an aqueous simulation solution) loaded as per the DP shipping process. The loaded shippers were subjected to the ((b) (4)) distribution simulation (a series of tests to assess physical damage that could affect thermal performance of the shipper) and exposed to a ((b) (4)) ambient ((b) (4)) profile (peak temperatures of ((b) (4)) at start and end of testing, with a prolonged hold at ((b) (4))). Internal temperature of the cryoshipper was monitored using calibrated monitoring and recording devices. Acceptance criteria were based on how long the loaded shipper could maintain an internal temperature of ((b) (4)) and whether damage to the freezing bags was observed. Results indicate that internal temperature was held below ((b) (4)); no damage occurred to the payload of freezing bags and the shipper maintained thermal integrity in the ((b) (4)) simulation. Based on this study, the ((b) (4)) shipper is qualified to hold a temperature of ((b) (4)).

Reviewer comment: Note that only shippers loaded with the maximum payload were evaluated in this study. Janssen's rationale for this is that the shipper system's minimum temperature is established by the temperature of liquid nitrogen and the payload chamber within the shipper is ((b) (4)). Therefore, a smaller payload (fewer bags) would not pose any additional risk that testing the maximum payload would not satisfy. This assessment is reasonable. Note also that only the ((b) (4)) profile (not the ((b) (4)) profile) was tested, as this represents the worst-case scenario for ambient ((b) (4)) exposure that could affect DP temperature. This is acceptable.

DP will be distributed by ((b) (4)) transportation at ((b) (4)) in the ((b) (4)) dry vapor cryoshipper (qualified passive system) using an internal shipping lane to ((b) (4)) (from Janssen, ((b) (4)) to ((b) (4)) and via external shipping lanes (from Janssen, ((b) (4)) or from Distribution Center ((b) (4)) to customers. To support use of these shipping lanes, real-time transportation studies were conducted to evaluate the potential impact of shipping conditions on DP quality and container closure integrity. DP lots consisting of low ((b) (4)) cells/mL) and high ((b) (4)) cells/mL concentrations in a 30 mL ((b) (4)) bag) or 70 mL ((b) (4)) bag) volume were manufactured at ((b) (4)). Product was ((b) (4)) shipped for ((b) (4)), and ((b) (4)) shipped for ((b) (4)) in ((b) (4)) dry vapor shippers. ((b) (4)) (T0) testing was performed, and ((b) (4)) of DP bags were tested after completion of shipping ((b) (4)), post-shipping) while a ((b) (4)) set of shipped bags were stored at $\leq -120^{\circ}\text{C}$ for ((b) (4)) and then tested ((b) (4)), post-shipping). Testing was performed using the ((b) (4)) methods in place at the time (except for dose as a specific patient weight is required for the dose calculation) including assessments of ((b) (4))

All acceptance criteria were met in all cases.

In addition, ((b) (4)) were tested with all results meeting acceptance criteria. ((b) (4)) was seen at ((b) (4)) post-shipping relative to T0 and initial post-shipping values, but acceptance criteria were still met and no concomitant ((b) (4)) were seen.

The effect of shock and vibration on container closure integrity (CCI) was evaluated by the (b) (4) test method following (b) (4)

the acceptance criteria were met.

Reviewer comment: Additional information was provided in Amendment 36 (response to CMC IR of 08/10/2021, received 08/23/2021) describing the bag defect observed after simulated transport. This

(b) (4)

This response is acceptable. Amendment 36 also clarified a typographical error in the footnote of CCIT acceptance criteria table (which originally read (b) (4) confidence and (b) (4) coverage but should have read (b) (4) confidence and (b) (4) coverage). These responses are acceptable.

Overall Reviewer’s Assessment of Section 3.2.P.3.5:

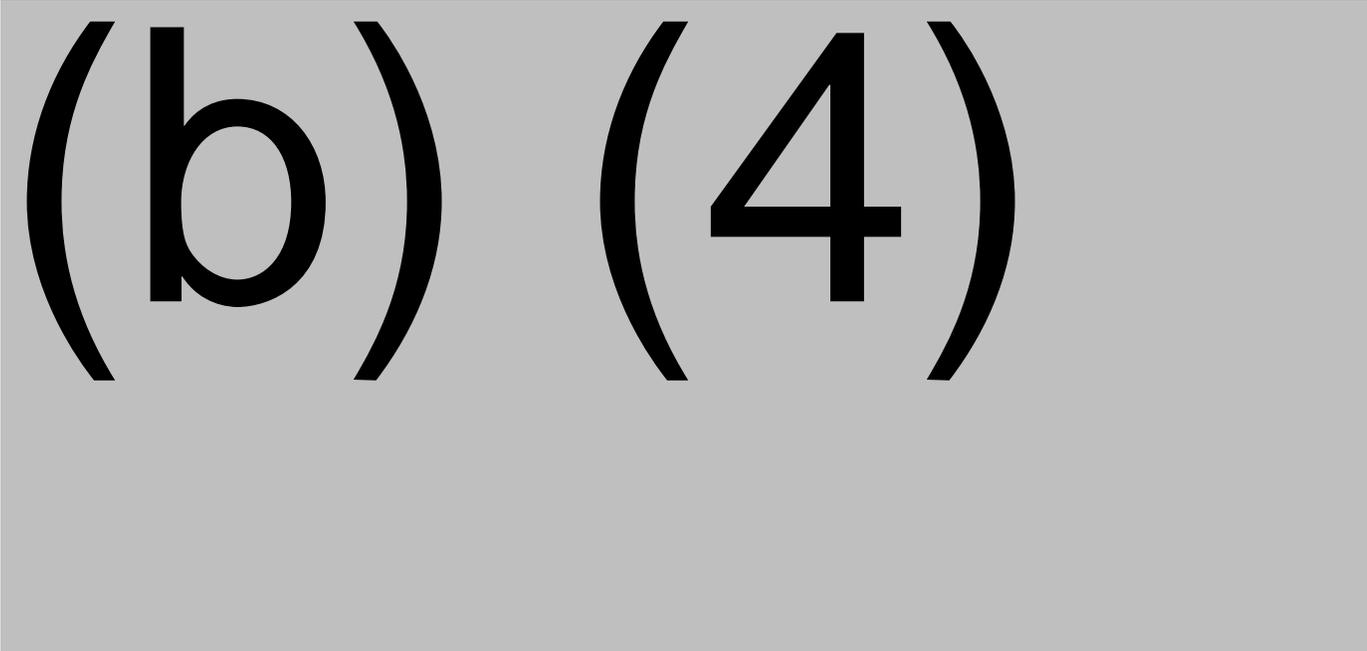
The qualification studies to support DP shipping in the (b) (4) dry vapor shipper are acceptable. The real time transportation studies demonstrate that product quality was not impacted by shipping DP over a considerable distance by (b) (4) (equivalent to land transport from (b) (4) to (b) (4) and back, and (b) (4)). This is further supported by thermal simulation studies that indicate the dry shipper can maintain an internal temperature of (b) (4) for almost (b) (4). The simulated transport sequence studies indicated that (b) (4). Corrective action to address this has been taken and is appropriate. Note that based on this information only the (b) (4) dry vapor shipper has been qualified. In several places in the BLA submission, Janssen states “passive shipping systems”. If additional shippers are proposed for use, the relevant qualification data should be provided and found acceptable before they are brought into service. This was communicated to Janssen in the CMC IR of 08/10/2021. Janssen acknowledged this in Amendment 36 (response to CMC IR, received 08/23/2021) and stated that the (b) (4) dry vapor shipper is the only shipping system in use and that any qualification data for alternate dry vapor shippers will be submitted to the BLA as appropriate. This is acceptable.

3.2.P.4 Control of Excipients

Reviewed by GEP

3.2.P.4.1 Specifications

The composition of the (b) (4) excipient is described in Section 3.2.P.2.1.2 Excipients. Test methods and acceptance criteria for release of (b) (4) performed by Janssen are shown in Table 73, and are conducted in addition to testing performed by the vendor as reported on the (b) (4) COA.



3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

(b) (4) methods are listed in Table ; non-compendial methods are described as follows:

- *Appearance and color* are assessed by (b) (4) noting color, clarity, homogeneity, and presence of any particulate matter. This test is performed by trained operators according to validated visual inspection methods.
- *Identity* is confirmed through the combination of (b) (4) testing, and validated DMSO content testing. Results are verified by external testing against acceptance criteria for these parameters that are unique to (b) (4).
- *DMSO content* is quantified by (b) (4). Samples and DMSO standard are (b) (4).

LLOQ and LOD were not required as the procedure is used to confirm a target DMSO concentration (5% in (b) (4)). All validation acceptance criteria were met as shown in Table 74.

Table 74. DMSO content (excipient) analytical procedure validation summary

Parameters	Acceptance criteria	Results	Pass/fail
Precision: repeatability (N = (b) (4))	(b) (4)		Pass
Precision: intermediate precision (N = (b) (4))			Pass

Parameters	Acceptance criteria	Results	Pass/fail
Linearity	(b) (4)	(4)	Pass
Accuracy and range			Pass
Specificity			Pass
			Pass

^a Accuracy acceptance criteria defined in the protocol were determined to be too narrow relative to tolerance based on the specification range of (b) (4) of nominal DMSO content. Accuracy results are considered acceptable based on documented investigation.

3.2.P.4.4 Justification of Specifications

Janssen justifies (b) (4) specifications based on overall product development, clinical experience, and regulatory guidances. Release testing for sterility, (b) (4), and endotoxin ensures microbial control for patient safety, while product is tested for key parameters (including (b) (4), (b) (4), DMSO content, (b) (4)) in conjunction with the vendor COA.

3.2.P.4.5 Excipients of Human or Animal Origin

The only excipient of animal origin in (b) (4) is (b) (4), manufactured from (b) (4) by an (b) (4) method. The (b) (4) is manufactured by (b) (4) produced from (b) (4) (sourced from healthy animals) by a (b) (4). Certifications have been provided from the supplier to ensure that the (b) (4) is free of transmissible spongiform encephalopathy agents.

3.2.P.4.6 Novel Excipients

Not applicable: there are no novel excipients in the DP.

Overall Reviewer’s Assessment of Section 3.2.P.4:
 The (b) (4) excipient is a widely used cryopreservation medium, similar to (b) (4) (except for a 5% rather than (b) (4) DMSO content) which is used in other approved CAR T cell products. Information regarding (b) (4) was acceptable as submitted, and no IRs were required during the review cycle. There are no concerns regarding excipients.

3.2.P.5 Control of Drug Product

Reviewed by GEP (except as otherwise noted).

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

Cilta-cel specifications are presented in Table 75. The timing of sample acquisition for each lot release test is shown in Table 76. Justification of each specification is provided in the narrative below.

Table 75. Lot release and stability acceptance criteria for cryopreserved DP

Attribute	Test parameter	Test method	Acceptance criteria	
			Release	Stability
General	Appearance of color	Visual examination	(b) (4)	(b) (4)
	Appearance of primary container	Visual examination	Each bag is without visible defects or leaks	Each bag is without visible defects or leaks
Safety	Sterility	(b) (4)	No growth	No growth
	Endotoxin	(b) (4)	(b) (4)	NA
	Mycoplasma	(b) (4)	Not detected	NA
	Replication-Competent Lentivirus	(b) (4)	(b) (4)	NA
	(b) (4)	(b) (4)	(b) (4)	NA
Purity	(b) (4) Viability	(b) (4)	(b) (4)	(b) (4)
	Phenotype (b) (4)	(b) (4)	(b) (4)	NA
	Phenotype (% NK)	(b) (4)	(b) (4)	NA
	Phenotype (b) (4)	(b) (4)	(b) (4)	NA
Identity	CAR Identity	(b) (4)	(b) (4)	NA
Quantity	Viable cell concentration	(b) (4)	(b) (4)	(b) (4)
Dose	Number of CAR ⁺ viable T cells per kg of patient weight of total CAR ⁺ viable T cells in the final container	Calculation ^b	Patient 100.0 kg or below: 0.5 – 1.0 × 10 ⁶ CAR ⁺ viable T cells/kg	Patient 100.0 kg or below: 0.5 – 1.0 × 10 ⁶ CAR ⁺ viable T cells/kg
			Patient above 100.0 kg: 0.5 – 1.0 × 10 ⁸ CAR ⁺ viable T cells	Patient above 100.0 kg: 0.5 – 1.0 × 10 ⁸ CAR ⁺ viable T cells
Potency / Identity	CAR expression from viable T cells	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)	(b) (4)

^a The calculation is based on results from (b) (4)

^b The calculation is based on results from (b) (4)

Reviewer comment: During the review cycle, commercial DP release specifications were modified from those originally submitted. The final specifications (as agreed with Janssen) are shown in Table 75. The (b) (4) potency assay, described in Amendment 56 (received 10/14/2021) replaces the original commercial (b) (4) assay, which will no longer be used. The originally proposed specification for (b) (4) by (b) (4) was found to be unnecessary (as (b) (4) [determined by calculation based on (b) (4) data] is more relevant and informative) and was removed in Amendment 40 (received 09/03/2021). The attribute classification for CAR expression was updated from Potency to Potency/Identity in Amendment 72 (received 01/07/2022) to reflect the ability of this assay to confirm product identity. These changes are acceptable.

Table 76. Timing of sample acquisition, test sites, and SOPs

Analytical method	Method test article		Test site	Method SOP
	Manufacturing stage	Description		
Appearance of color	(b) (4)	Final DP	Janssen ^{a, b, c}	TV-TMD-13758
Appearance of primary container		Final DP	Janssen ^{a, b, c}	TV-TMD-00652
Sterility		Final DP	Janssen ^a	TV-TMD-34313
				N/A ^f
Endotoxin		Final DP	Janssen ^{a, c}	TV-TMD-31282
Mycoplasma		(b) (4)	(b) (4) ^e	N/A ^f
Replication-competent lentivirus (RCL)		(b) (4)	Janssen ^a	TV-TMD-33726
		(b) (4) sample		
(b) (4)		(b) (4) sample	Janssen ^{c, d}	N/A ^g
(b) (4) viability		Final DP	Janssen ^{a, c, d}	TV-TMD-33913
Phenotype (b) (4)		Final DP	Janssen ^{a, c, d}	TV-TMD-33314
Phenotype (% NK)		Final DP	Janssen ^{a, c, d}	TV-TMD-33314
Phenotype (b) (4) purity		Final DP	Janssen ^{a, c, d}	TV-TMD-33314
CAR identity		(b) (4) sample	Janssen ^{a, c, d}	TV-TMD-17630
Viable cell concentration		Final DP	Janssen ^{a, c, d}	TV-TMD-17630
Number of CAR ⁺ viable T cells per kg of patient weight, or total CAR ⁺ viable T cells in final container		Final DP	Janssen ^g	N/A ^g
CAR expression		Final DP	Janssen ^{a, c, d}	TV-TMD-33314
(b) (4)		Final DP	Janssen ^{c, d}	TV-TMD-34993

SOP: Standard Operating Procedure; DP: Drug Product; N/A: Not applicable

- ^a Janssen Pharmaceuticals, Inc., (b) (4) (JSC-QC)
- ^b Janssen Pharmaceuticals, Inc., (b) (4) ((b) (4) Ops.)
- ^c Janssen Biotech, Inc., (b) (4) (JSC-QC)
- ^d Janssen Biotech, Inc., (b) (4) (BioTD)
- ^e (b) (4)
- ^f Cross-referenced to (b) (4)
- ^g Method is a calculation

Reviewer comment: Additional information regarding test sites conducting each assay was provided in Amendments 3 (received 06/30/2021 in response to the CMC IR of 06/22/2021), 56 (received 10/14/2021), and 64 (received 11/15/2021). This information has been incorporated into Table 76, and is acceptable.

Justification of Specifications: Overview

DP acceptance criteria for quantitative attributes were established based on statistical analysis of release data from lots used in the MMY2001 study that resulted in effective clinical responses (partial response or better). The statistical analysis used the tolerance interval approach (one or two sided) with (b) (4). Acceptance criteria for qualitative attributes (color, appearance, sterility, etc.) were established based on compendial and/or regulatory guidelines rather than by statistical analysis. Quantity and dose are calculations based on patient weight. Therefore, statistical evaluations of these parameters were not performed. The justification for each DP specification is outlined below.

Reviewer comment: Originally, Janssen utilized a Bayesian statistical analysis to set (b) (4) acceptance criteria using prediction intervals based on release results from (b) (4) DP lots (b) (4) clinical lots from multiple clinical studies, (b) (4) process validation lots, and (b) (4) commercial stability lots), all of which were manufactured using patient apheresis material. However, this analysis was not reflective of

manufacturing experience under the pivotal MMY2001 study, and the (b) (4) prediction interval approach was assessed to result in overly broad acceptance criteria. To ensure that commercial product acceptance criteria were in the range seen during the MMY2001 study, FDA requested that Janssen calculate acceptance criteria based on the tolerance interval approach with (b) (4) confidence and (b) (4) coverage using data from MMY2001 lots that gave effective clinical responses (as described above). Batch analysis information (reviewed in Section 3.2.P.5.4 Batch Analyses) indicated that clinical lots produced at the (b) (4) , (b) (4) , and (b) (4) sites were similar, supporting (b) (4) of these lots for the purposes of specification setting. Multiple interactions were conducted with the applicant during the review cycle, resulting in the final acceptance criteria and justification of specifications submitted in Amendment 56 (received 10/14/2021) and confirmed in Amendment 64 (received 11/15/2021).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer’s Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:
 Analyses attempting to correlate DP quality attributes with clinical outcomes (overall response, CRS and neurotoxicity) revealed no significant relationship between these parameters. These findings are similar to those seen for other CAR T cell products. However, a potential limiting factor in this instance is related to the high clinical effectiveness of cilta-cel in the MMY2001 study, where (b) (4) lots resulted in a PR or better, meaning that parameters associated with lack of effectiveness cannot be identified. Data used in these analyses was provided in Amendment 36 (received 08/23/2021), which included tabulated lot release results from the MMY2001 study with associated grades of CRS and neurotoxicity and clinical response (Janssen’s assessment). This corresponds with the “all treated” MMY2001 clinical dataset from Amendment 2 submitted 02/02/2021. Extensive interactions to clarify and review DP commercial acceptance criteria were held with Janssen throughout the review cycle, as outlined in the review body. DP commercial acceptance criteria were finalized in Amendment 64 received 11/15/2021 and are appropriately justified using relevant statistical analyses where appropriate. There are no outstanding concerns.

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

Appearance of Color (Test method TV-TMD-13758)

Color of the DP suspension in the final container is assessed by qualified operators using the (b) (4) method. In addition, the bag is examined for (b) (4)

immediately after filling within the manufacturing suite. Presence of any (b) (4) in the final DP is subject to further investigation prior to batch disposition. The method was verified under actual conditions of use at JSC-QC (b) (4) JSC-QC (b) (4), and (b) (4) Operations by (b) (4) operators on (b) (4) days using both (b) (4) bags.

Reviewer comment: Assessment of particulates and clumps was described in Amendment 16 (response to CMC IR of 06/22/2021 received 07/07/2021) and is acceptable. This method is suitably qualified for use.

Primary Container (Test method TV-TMD-00652)

The DP bag is visually examined prior to (b) (4).

The entire DP bag is (b) (4)

and transferred to JSC-QC-CAR-T (b) (4). Verification studies were under conditions of actual use were performed at JSC-QC (b) (4) Operations, and JSC-QC (b) (4). All 3 sites are qualified for DP testing using this method.

Sterility

Reviewed by DBSQC

Sterility testing uses a validated (b) (4) system using (b) (4)

(b) (4). If no positive result is detected for (b) (4), the samples are determined to be negative for microbial growth.

Reviewer comment: The DBSQC reviewer (Karla Garcia CBER/OCBQ/DBSQC) concludes that the (b) (4) method is suitable for its intended use and validated in accordance with (b) (4). There are no concerns with this method.

Endotoxin

Reviewed by DBSQC

Endotoxin levels in DP are determined by a (b) (4)

. Assay is considered valid if the correlation coefficient of the standard curve is (b) (4) and the inhibition control value is between (b) (4).

Reviewer comment: The DBSQC reviewer concludes that the endotoxin test method is compliant with (b) (4) and is acceptable. There are no concerns with this method.

Mycoplasma

Reviewed by DBSQC

The mycoplasma assay is a (b) (4) method using (b) (4)

. Testing is performed on a sample taken (b) (4) steps. The lower detection limit is (b) (4).

Samples are assessed as positive if (b) (4).

Reviewer comment: The DBSQC reviewer concludes that the mycoplasma (b) (4) test method was validated in accordance with (b) (4) and is acceptable for its intended use. There are no concerns with this method.

(b) (4) Viability and Viable Cell Concentration (Test method TV-TMD-33913)

Viable cell concentration and (b) (4) viability are assessed using the (b) (4)

For the assay and results to be valid, all replicate reads must meet defined system suitability criteria. This method is used for final cryopreserved DP, (b) (4) samples taken (b) (4), as shown in Table 79.

Table 79. DP (b) (4) viability and cell concentration testing

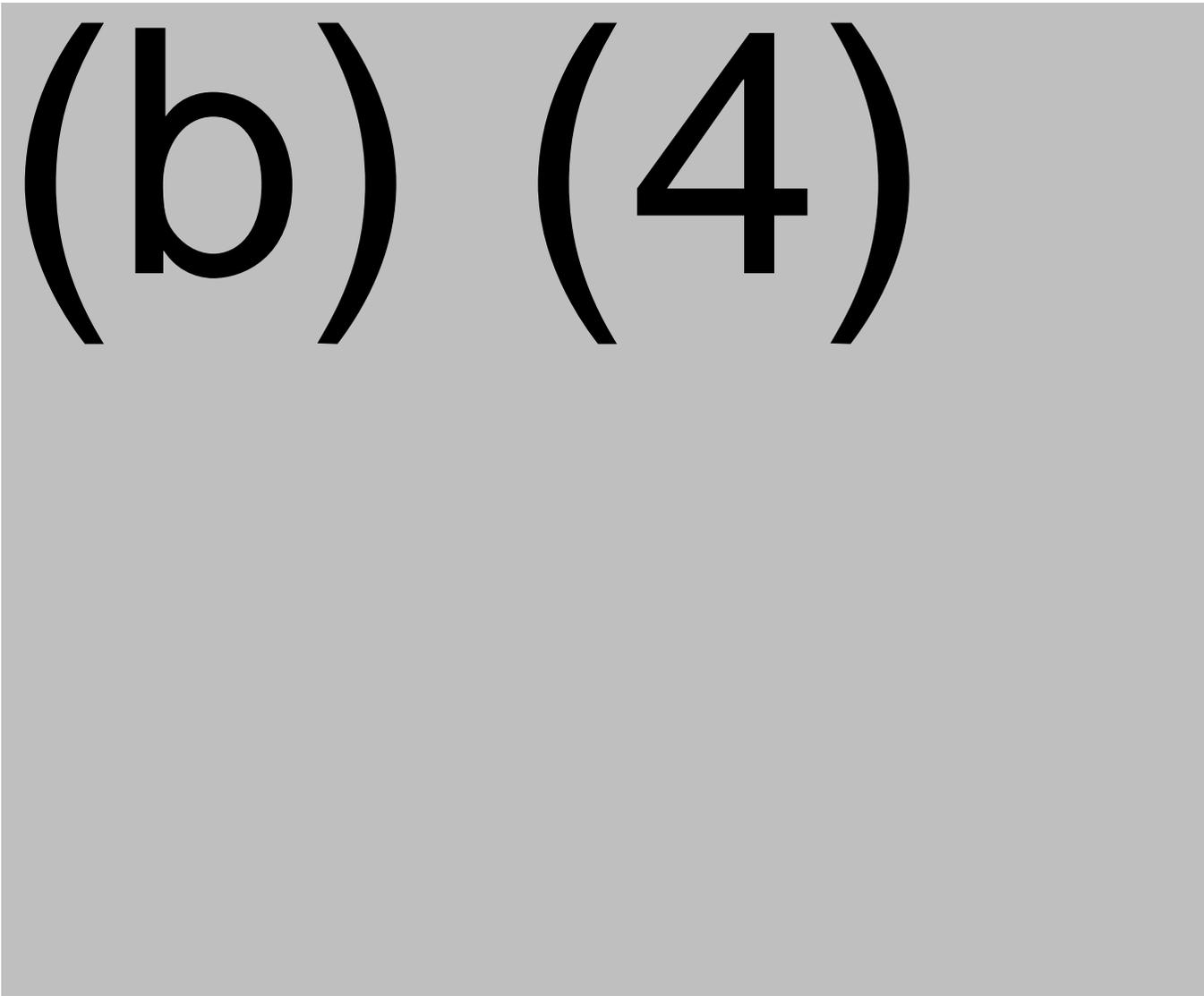
Sample	Replicates	Notes	Data reporting
(b) (4)	(4)		

Sample	Replicates	Notes	Data reporting

This assay method was primarily validated at (b) (4) and co-validated at JSC-QC (b) (4) and JSC-QC (b) (4). ...Validation studies used (b) (4) DP lots as test articles. Specificity (viable or non-viable cells) was assessed by (b) (4). Accuracy was assessed by (b) (4); this data was also used to assess linearity and assay range. Repeatability was assessed by (b) (4). Laboratory equivalence was determined on viable cell count and viability data from the DP precision studies at each site by two one-sided test (TOST) to define (b) (4) Bayesian credible intervals (CI) of the mean difference between (b) (4) and each co-validation site; for laboratories to be considered equivalent, these CI values must be within (b) (4) boundaries. Stability indicating properties of the assay were determined by (b) (4). Robustness assessments examined effect of (b) (4). Assay validation acceptance criteria and results are summarized in Table 80.

Table 80. Summary of acceptance criteria and validation results for cell count and viability analytical procedure

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There were no deviations or invalid assays during the validation studies.

Reviewer comment: Note that validation acceptance criteria for this (and other assays) were relatively broad (e.g., (b) (4) , as opposed to $\leq 20\%$ CV which commonly used). Using such wide criteria may lead to acceptance of higher assay variability than would otherwise be the case. However, actual results obtained in validation studies were substantially below the acceptance criteria in almost all cases, demonstrating acceptable assay performance. Validation of the viable cell count method has been acceptably demonstrated in the range (b) (4) cells/mL at all 3 sites. In addition to lot release testing, this method will be used as an (b) (4) test. There are no concerns with this method or system/sample suitability criteria.

Replication Competent Lentivirus (RCL: Test method TV-TMD-33726)

Absence of RCL in the final product is determined by a (b) (4) assay for (b) (4)

(b) (4)

Reviewer comment: Qualification of (b) (4) assay standards was described in detail in Amendment 13 (received 06/30/2021 in response to the CMC IR of 06/22/2021). This information is reviewed in 3.2.P.6 Reference Standards or Materials.

The assay is analyzed (b) (4)

Reviewer comment: As described in Amendment 13 (received 06/30/2021 in response to the CMC IR of 06/22/2021), test article (b) (4) is prepared independently for each of the (b) (4) assays (the RCL (b) (4) assay, the (b) (4) assay, and the CAR identity (b) (4) assay) from individual samples as part of each assay procedure in the same QC lab where the assay is performed. This is acceptable.

Results are documented as follows:

(b) (4)

(b) (4)

Results from this equation are reported for each DP lot as shown in Table 81.

Table 81. Results reporting for DP RCL (b) (4) test

(b) (4)

(b) (4)

Reviewer comment: Information in this table was clarified in Amendment 13 (received 06/30/2021 in response to the CMC IR of 06/22/2021), and typographical errors were corrected. This response was acceptable. There are no concerns with this method or system/sample suitability criteria.

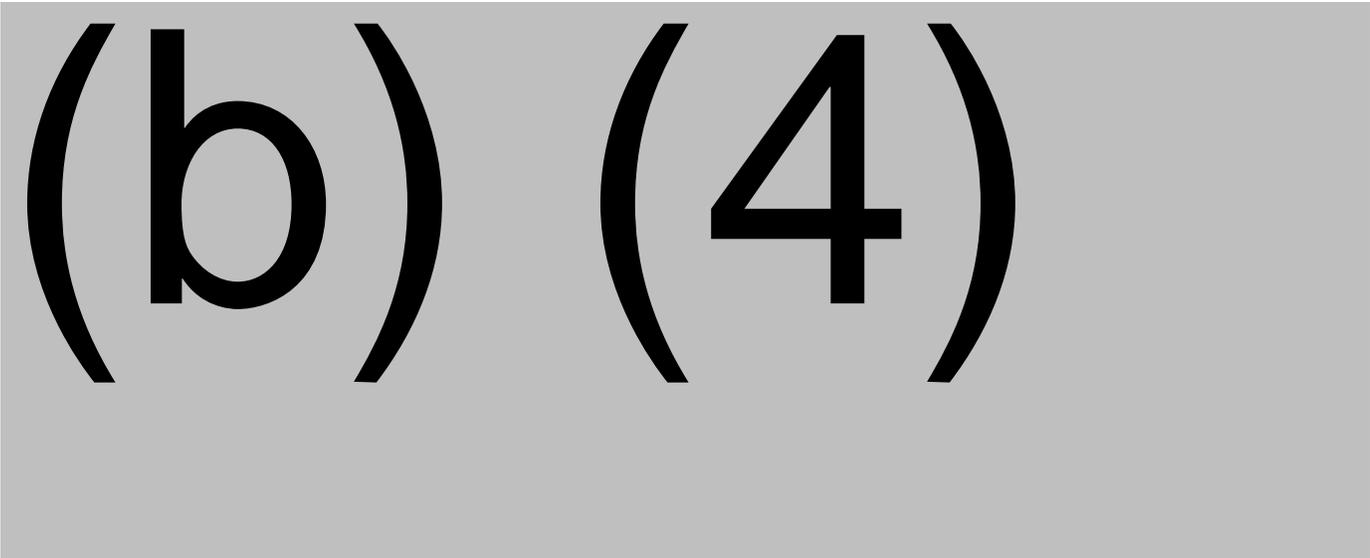
The (b) (4) method was primarily validated at (b) (4) and co-validated at JSC-QC (b) (4)

[Redacted content]

Assay validation parameters and results are summarized in Table 82, robustness parameters are described below.

Table 82. Summary of acceptance criteria and validation results for (b) (4) (RCL) analytical procedure

(b) (4)



Reviewer comment: Table footnotes were clarified in Amendment 17 (response to CMC IR of 07/09/2021, received 07/19/2021). This amendment also clarified that intermediate precision was assessed by (b) (4) operators over (b) (4) days at (b) (4), (b) (4) operators across (b) (4) days at JSC-QC (b) (4), and (b) (4) operators across (b) (4) days at JSC-QC (b) (4). This is acceptable.

Robustness assessments included varying (b) (4) [redacted] None of these variations had an impact on (b) (4) assay performance.

In the co-validation study, the (b) (4) site met all of the required validation acceptance criteria and can be considered fully validated for testing (b) (4) DP test articles within the range of (b) (4) with an assay quantitative range of (b) (4) and a LOD of (b) (4) and a quantitative range of (b) (4). However, validation failed for (b) (4) linearity/accuracy at the (b) (4) site, and for intermediate precision at the JSC-QC (b) (4) site.

In an attempt to address the failed validation at (b) (4) and JSC-QC (b) (4), supplementary validation studies were performed. (b) (4) [redacted]

(b) (4) ; as the assay remains fully validated at JSC-QC (b) (4), this should remain the only test site.

Reviewer comment: The supplemental validation study (submitted in Amendment 57, received 10/14/2021) revealed high variability between sites. Lot release testing using this method may only be performed at the JSC-QC-CAR-T (b) (4) laboratory where it was, and remains, successfully validated. Note that initial validation studies used a (b) (4) point standard curve, but the assay for lot release uses a (b) (4) point standard curve covering the range (b) (4) and (b) (4). As the (b) (4) point curve overlaps the validated assay range this is acceptable.

(b) (4)

[Redacted text block]

(b) (4)

(b) (4)

DP Phenotype Purity and CAR Expression (Test method TV-TMD-33314)

Ciltacel DP purity (b) (4) % NK, and (b) (4)) and CAR expression is assessed by (b) (4)

Reviewer comment: The (b) (4) acceptance criteria of (b) (4) expression (b) (4) was clarified in Amendment 13 (received 06/30/2021 in response to the CMC IR of 06/22/2021) and refers to (b) (4) of the (b) (4) value (i.e., for (b) (4) expression the acceptable range would be (b) (4) . This is acceptable.

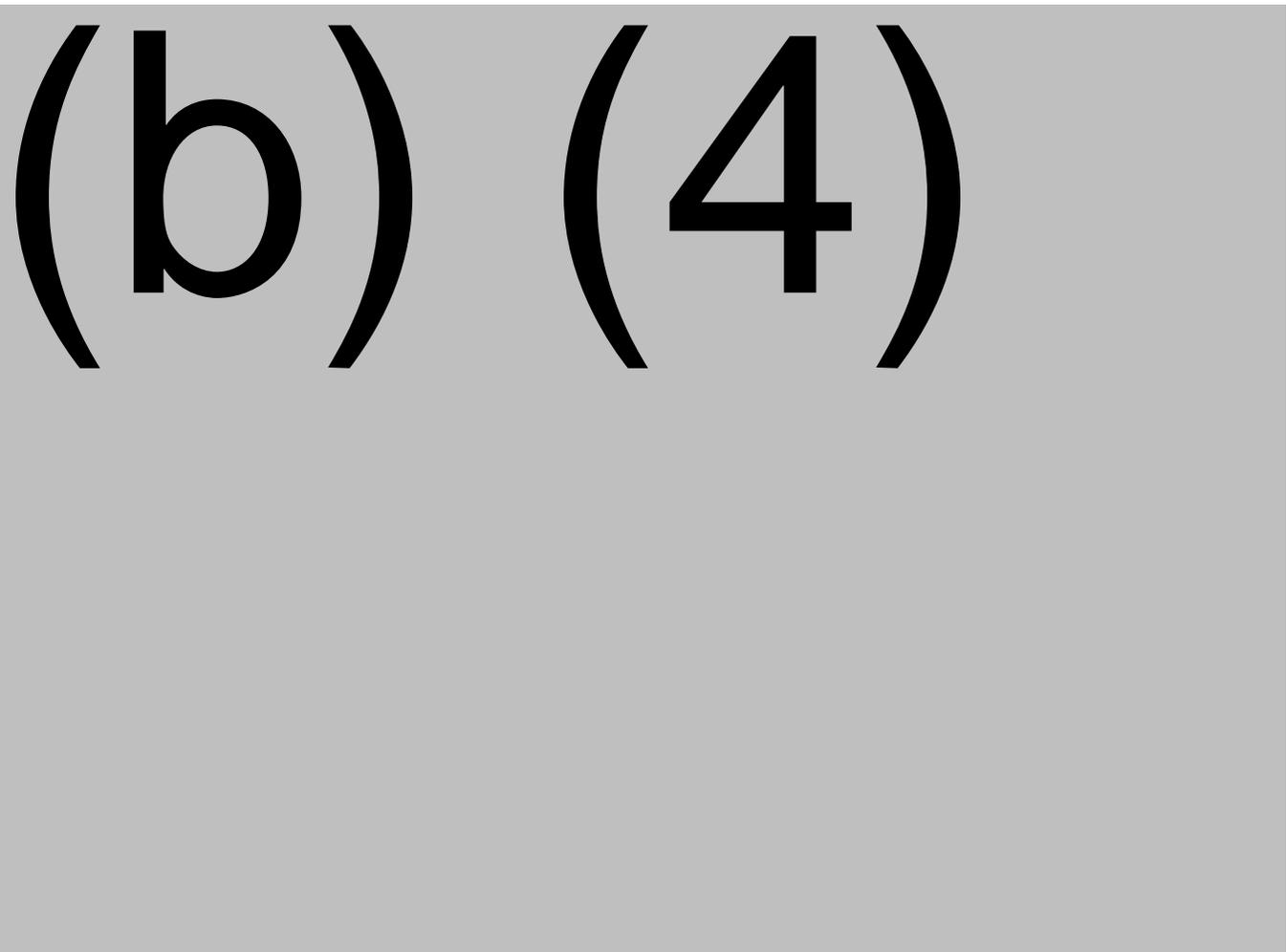
(b) (4)

Reviewer comment: In Amendment #17 (response to CMC IR of 07/09/2021, received 07/19/2021), the use of (b) (4) [redacted] for validation studies was justified by noting that the (b) (4) [redacted] prior to analysis would result in (b) (4) [redacted] potentially resulting in (b) (4) [redacted]. The use of (b) (4) [redacted] is thus a worst-case scenario. Data comparing (b) (4) [redacted] and % CAR expression results from (b) (4) [redacted] (obtained during PPQ studies) and (b) (4) [redacted] (obtained during assay validation studies) for the same lots was also provided in Amendment 17. Results were in close agreement (differences (b) (4) [redacted] in each case) and within assay variability. These responses are acceptable.

The key experimental design for specificity and accuracy/linearity parameters (which were assessed simultaneously in the same experiments) was to perform (b) (4) [redacted]

[redacted] Range and precision were determined from the accuracy/linearity data. LLOQ was determined for NK and (b) (4) [redacted], and the stability-indicating properties of the assay were assessed using (b) (4) [redacted]

[redacted] Equivalence testing between the laboratories was conducted by analyzing accuracy and precision assays at each site using TOST and calculating the (b) (4) Bayesian CI on the differences in (b) (4) [redacted] among sites; if this interval was contained within equivalence boundaries of (b) (4) [redacted] the two laboratories were deemed equivalent. Assay validation parameters and results are summarized in Table 84.



(b) (4)

Note that the assay range for NK cells was determined to be (b) (4) but the originally proposed specification for % NK cells was (b) (4) which is out of this range. The % NK cell specification was subsequently revised to (b) (4) resolving this concern.

Reviewer comment: This assay has been validated for assessment of T-cell purity, CAR expression, and impurities (NK (b) (4)), showing acceptable specificity, linearity, precision and linear range at all 3 test sites. Acceptance criteria for robustness parameters were provided in Amendment 17 (response to CMC IR of 07/09/2021, received 07/19/2021) and are acceptable. Note that some robustness parameters resulted in large % difference values for (b) (4) NK cells due to these populations being below LLOQ. These findings are mathematic artifacts and do not affect assay performance or validation. A secondary review of the (b) (4) method validation was conducted by Jing Lin (CBER/OCBQ/DBSQC) and concludes that the (b) (4) assay has been appropriately validated for use. This is in agreement with the conclusions reached here. There are no outstanding concerns.

DP CAR Identity (Test method TV-17630)

Ciltacel DP identity is determined by a (b) (4) assay with (b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

The test article CAR identity is reported as positive for lentivector integration if (b) (4) [Redacted] is observed above the assay threshold in all replicates

Reviewer comment: During clinical development this method was used to assess (b) (4) for lot release, but (b) (4) results were seen when LVV manufacture was changed from (b) (4) process to a (b) (4) process (see 3.2.S.2.6 Manufacturing Process Development Analytical development history). Thus, the (b) (4) assay was replaced with the (b) (4) assay for determination of (b) (4) at lot release, but the (b) (4) assay was retained as an identity test for lot release. Note that (b) (4) calculated based on (b) (4) is not part of the lot release acceptance criteria. These issues were clarified in Amendment 13 (received 06/30/2021 in response to the CMC IR of 06/22/2021). There are no concerns with this method or system/sample suitability criteria.

The CAR identity method was primarily validated at (b) (4) and co-validated at JSC-QC (b) (4) and JSC-QC (b) (4). Validation studies used (b) (4)

[Redacted]

[Redacted] was used for specificity studies. Assay validation experiments followed a similar strategy to those described for the (b) (4) assay and are summarized in Table 85; robustness parameters are described below.

(b) (4)

(b)

(4)

Robustness parameters assessed included varying the (b) (4)

(b) (4)

(b) (4) invalid assays occurred during co-validation at JSC-QC (b) (4) . (b) (4) , causing the assay to fail acceptance criteria; this assay was repeated with no issues. (b) (4)

No other deviations were reported.

Reviewer comment: Analyst errors are a common problem with (b) (4) assays but were detected by routine quality control measures (rigid assay acceptance criteria). These errors do not affect the overall assay validation process, and there are no concerns. The (b) (4) (CAR identity) assay can therefore be considered adequately validated at (b) (4) , JSC-QC (b) (4) , and JSC-QC (b) (4).

Number of CAR-positive Viable T Cells

This calculation determines the total transduced viable T cells (representing the active ingredient of the DP) that will be administered to patients. The dose is calculated using (b) (4) as determined using the DP (b) (4) methods, respectively, along with patient weight information. The total viable cells per bag is based on total viable cell concentration and the bag fill volume. Calculations for patients below (Equation 9) and above (Equation 10) 100.0 kg are shown below:

Equation 9. Dose calculation for patients 100.0 kg or below

$$\text{Dose} = \frac{\text{(b) (4)}}{\text{patient weight [kg]}} \times \text{volume per bag [mL]}$$

Equation 10. Dose calculation for patients above 100.0 kg

$$\text{(b) (4)} \times \text{volume per bag [mL]}$$

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer’s Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

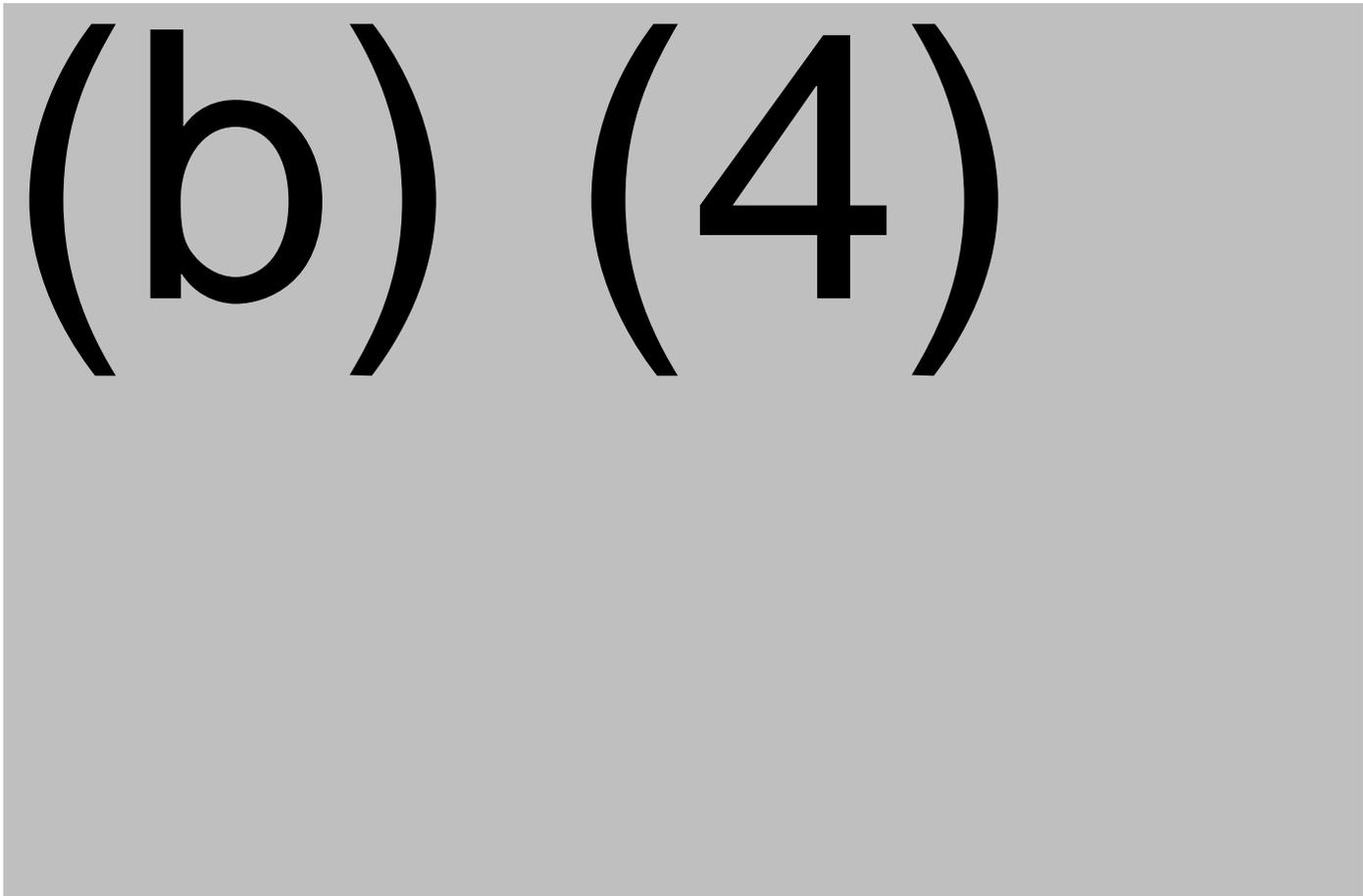
Assay methods are suitable and adequate to ensure product safety, identity, purity, and potency. Validation of analytical methods for commercial DP lot release testing has been performed adequately, with the following exceptions: 1.) Co-validation of the RCL (b) (4) assay was unsuccessful at the (b) (4) and JSC-QC (b) (4) sites; until successful assay validation is performed at these sites and laboratory equivalence between sites is demonstrated this assay may only be performed for commercial lot release testing at the JSC-QC (b) (4) site. 2.) The (b) (4) (potency) assay is validated at the (b) (4) and JSC-QC (b) (4) sites and may be performed for commercial lot release testing at these sites. If any additional sites are to be added for testing for this (or any other assay), updated validation data must be provided for review prior to initiation of testing at the new site. Janssen were informed of these issues in CMC IR #13, sent 11/10/2021. This was acknowledged in Amendment 64 (received 11/15/2021), where Janssen committed to submit any post-approval additions of testing laboratories as a CBE-30.

Extensive interactions were held with Janssen during the review cycle, especially regarding the potency assay (as outlined above and in Section 3.2.S.2.6 Manufacturing Process Development, (b) (4) (potency) method changes) resulting in replacement of the (b) (4) assay with the current (b) (4) potency assay. The submission of information in Amendment 56 regarding validation of the (b) (4) assay at the commercial test site, justification of (b) (4) release specifications, and updated batch analysis data late in the review cycle necessitated a major amendment to be issued, extending the review clock. All concerns (other than the minor issues related to site-specific assay validation noted above) have been adequately addressed and resolved.

3.2.P.5.4 Batch Analyses

Batch analysis information is summarized in Table 87. This data includes 97 lots administered to patients in the MMY2001 study, of which (b) (4) were produced at (b) (4) at (b) (4), and (b) (4) at (b) (4). Also presented are (b) (4) clinical lots produced at (b) (4); these lots include the (b) (4) administered in MMY2001 as well as an additional (b) (4) manufactured for use in Japan produced and (b) (4) MMY2001 lots that were not administered due to study ineligibility, deaths, withdrawals etc. Also included in the (b) (4) (b) (4) clinical lots are (b) (4) from the MMY2003 study, (b) (4) from MMY3002, and (b) (4) from MMY4003; these

latter ^(b)(4) studies are for different indications or patient populations than the pivotal MMY2001 study. All lots shown in Table 87 met acceptance criteria for qualitative (appearance, identity) and safety (sterility, mycoplasma, endotoxin, and ^(b)(4) RCL) parameters.



⁹ Dose specification is $0.5 - 1.0 \times 10^6$ CAR⁺ viable T cells/kg for patients ≤ 100 kg and $0.5 - 1.0 \times 10^8$ CAR⁺ viable T cells for patients > 100 kg

Reviewer comment: *The batch analysis data from the MMY2001 study indicate that product lots produced at the ^(b)(4) , ^(b)(4) , and ^(b)(4) sites are very similar; in general, results from ^(b)(4) and ^(b)(4) fall within the observed range seen for MMY2001 lots manufactured at ^(b)(4) although there are individual outliers for ^(b)(4) . This similarity between sites supports pooling of lot release data from the MMY2001 study for use in specification setting. Note that all 97 MMY2001 lots were produced with LVV manufactured at ^(b)(4) . While all 97 MMY2001 clinical met acceptance criteria in place at the time of release for use under IND, ^(b)(4) would have failed the subsequently established commercial acceptance criteria ^(b)(4) for viability, ^(b)(4) for viability and % NK cells, ^(b)(4) for % NK cells, ^(b)(4) for % NK cells ^(b)(4) ; an additional ^(b)(4) lots could not be assessed for ^(b)(4) as no retain samples were available. While this appears to be a relatively high failure rate, it is not unexpected given that specifications were set based on ^(b)(4) confidence, ^(b)(4) coverage tolerance intervals from the ^(b)(4) lots of this 97 that resulted in a partial response or better. As it is Janssen’s standard practice to manufacture a new product lot from retained apheresis material in the event of a failed release test result, the effective manufacturing failure rate (at the patient level) will likely be considerably lower although delays in treatment may occur.*

The “All (b) (4) clinical lots” batch information is included as these lots are likely to be more representative of future product (as all were manufactured at the commercial site, many were manufactured more recently than the MMY2001 lots, and a subset [N = (b) (4)] was produced using the (b) (4) LVV). Of note, clinical lots made using the (b) (4) LVV had a (b) (4) (b) (4) than those using the (b) (4) LVV (b) (4) (b) (4), which would result in an OOS (b) (4) result for (b) (4) lots made using the (b) (4) LVV compared to (b) (4) for the (b) (4) LVV. However, as the (b) (4) procedure was updated during the BLA review cycle to improve accuracy, there is insufficient information to assess whether this trend will continue. Note that the lots made using the (b) (4) LVV were for studies MMY2003 and MMY3002 which are for different patient populations (indication and pre-treatment histories, which may impact the quality of the T cells for transduction) than the MMY2001 study. Despite the (b) (4) results, all lots were below the currently recommended (b) (4) and do not represent a safety concern. From all (b) (4) clinical lots, a total of (b) (4) would have failed to meet commercial acceptance criteria for one or more parameters. This OOS rate is similar to that for the MMY2001 study, and the same caveats described above apply.

In addition to clinical lots, data from the (b) (4) process validation lots and (b) (4) commercial stability lots, all of which were manufactured with (b) (4) LVV, are relevant for assessing current manufacturing consistency. Data from these lots is summarized in Table 88.

Table 88. Batch analysis data from PV and commercial stability lots

Parameter	Commercial acceptance criteria	Range (mean ± SD; N)
(b) (4) viability	(b) (4)	(b) (4)
(b) (4)		
(b) (4)		
% NK cells		
(b) (4)		
% CAR+		
(b) (4)		
Dose	0.5 – 1.0 × 10 ⁶ CAR+ viable T cells/kg for patients ≤ 100 kg and 0.5 – 1.0 × 10 ⁸ CAR+ viable T cells for patients > 100 kg	(b) (4)

^a (b) (4) was assessed on retain samples for (b) (4) PV lots

^b Dose information is unavailable for the 2 commercial stability lots

Reviewer comment: All PV and commercial stability lots met commercial acceptance criteria for viability, purity, and CAR expression. Potency ((b) (4)) data is only available for (b) (4) PV lots, all of which met acceptance criteria. However, while it met acceptance criteria in place at the time, (b) (4) would not have met (b) (4) or dose commercial acceptance criteria, giving a failure rate of (b) (4) which is similar to that described above.

3.2.P.5.5 Characterization of Impurities

Product and process related impurities are described in 3.2.S.3.2 Impurities.

Overall Reviewer’s Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

Batch analysis information provided in the OS was supplemented with additional information provided in Amendments # 36 (received 08/23/2021) and #56 (received 10/14/2021). Overall, batch analysis information indicates that lots manufactured at the 3 different sites for use in the MMY2001 study were similar, supporting the pooling of this data for specification setting purposes. Taking into account all lots produced at (b) (4) (the commercial manufacturing site) the manufacturing process appears consistent, with an apparent lot failure rate (b) (4). Due to remanufacturing from (b) (4) apheresis material the actual clinical lot failure rate will likely be substantially lower and OOS lots may be released under IND as part of an expanded access program, minimizing risk to patients from product unavailability. A potential concern is that (b) (4) may be higher with the (b) (4) LVV than the (b) (4) LVV. While this does not represent a safety concern, it could result in an increased number of OOS lots. This should be monitored and specifications adjusted if necessary. There are no concerns with product- or process-related impurities.

3.2.P.6 Reference Standards or Materials

Reviewed by GEP

CAR identity (b) (4) standards

(b) (4)

(b) (4)

(b) (4)

RCL (b) (4) standards
(b) (4)

Positive control (QC) CAR T cells for CAR expression and (b) (4) assays

These cells are manufactured using the DP manufacturing process, (b) (4). Qualification of these control cells is performed as described in 3.2.P.5.2 and 3.2.P.5.3 Analytical: DP Phenotype Purity and CAR Expression (Test method TV-TMD-33314).

Reviewer comment: Additional details regarding generation and qualification of (b) (4) assay standards and controls was provided in Amendment 14 (response to CMC IR of 06/22/2021, received 07/01/2021). However, the assay acceptance criteria for slopes of the standard curves differed from those provided in the method descriptions. This discrepancy was resolved in Amendment 36 (received 08/23/2021 in response to CMC IR of 08/10/2021), which confirmed that the IR response was a typographical error; standard curve slopes must be (b) (4) per the method description. The description and qualification procedures for reference materials are acceptable.

3.2.P.7 Container Closure System

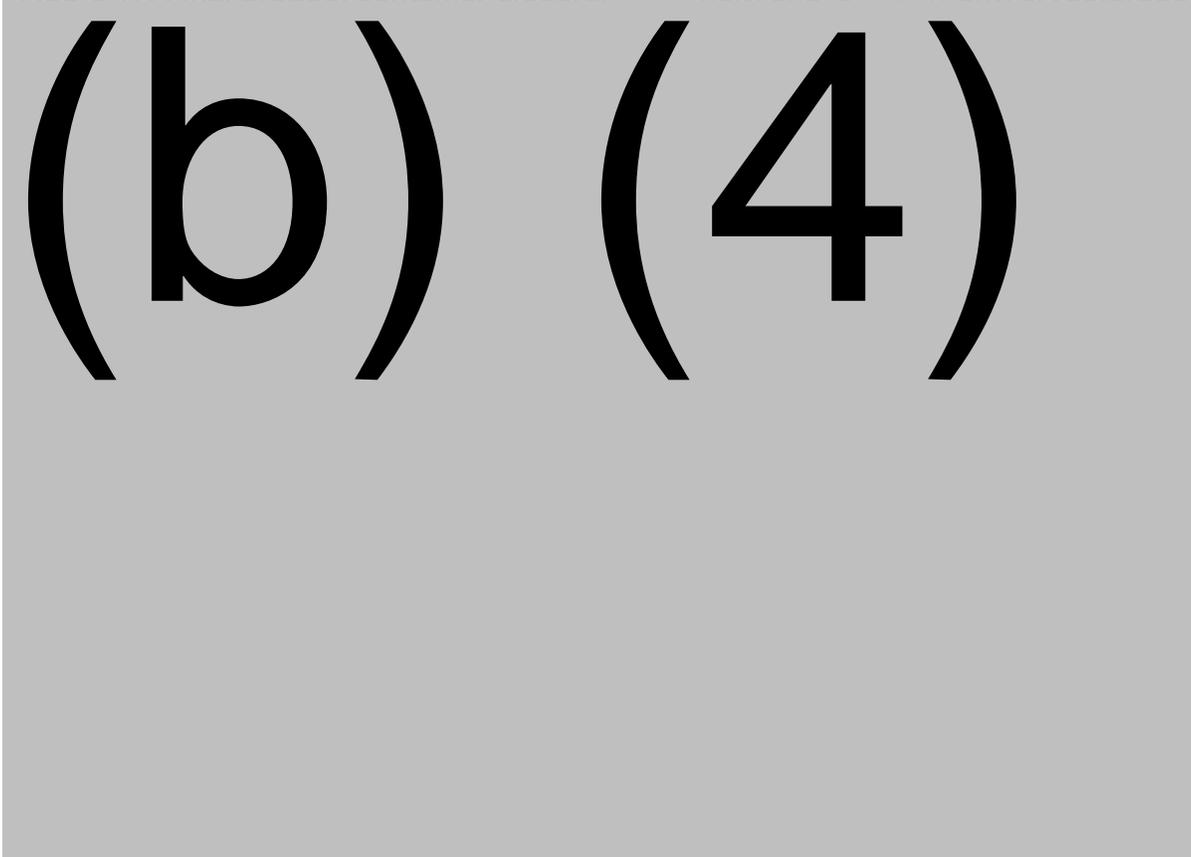
Reviewed by GEP.

The primary container closure systems for the cilta-cel DP are commercially available 510(k) cleared (b) (4) freezing bags ((b) (4)); Table 89 and Figure 17). The same bags are used for cryogenic storage of (b) (4) material. These cryostorage bags are classified per 21 CFR 864.9100 as FDA Class II medical devices used for blood component storage and delivery. The bags are constructed of ethylene vinyl acetate (EVA) film and the tubing set is an EVA/PVC co-extrusion. The bags are certified for use per (b) (4) class (b) (4) and (b) (4) testing. These bags are placed in an aluminum cryocassette ((b) (4)); Table 89) as a secondary container for protection during storage and shipping

Table 89. Description of final product container closure systems

Component	Packaging level	Description	Manufacturer
Freezing bag	Primary	(b) (4) ethylene vinyl acetate (EVA) freezing bag, (b) (4) 30 mL (b) (4) mL nominal fill volume)	(b) (4)
Freezing bag	Primary	(b) (4) ethylene vinyl acetate (EVA) freezing bag, (b) (4) 70 mL (b) (4) mL nominal fill volume)	
Cryo cassette	Secondary	(b) (4), aluminum, clear anodized, hinged with locking arm	
Cryo cassette	Secondary	(b) (4), aluminum, clear anodized, hinged with locking arm	

Figure 17. Final product container closure: (b) (4) (left) and (b) (4) (right) crvostoragee bags



Each incoming lot of primary packaging materials (freezing bags) and cassettes must comply with general visual inspection acceptance criteria before it is released for use. This initial inspection includes examination for physical damage to shipping containers and verification of the certificate of conformance [COC] and label information for the shipment and bags. The freezing bag COC details conformance of materials of construction, biocompatibility, sterilization, and seal integrity. The cassette COC details conformance of materials of construction, dimensions, and cleanliness.

Following the initial inspection, visual and physical inspections and functional tests are performed on the incoming freezing bags, as follows:

- *Visual inspection:* Bags are inspected for product identification, physical defects (e.g., (b) (4) [redacted]). The bags must meet a defined acceptable quality level (AQL).
- *Physical inspection:* Critical dimensions ($11.4 (b) (4) \times 7.6 \pm (b) (4)$ for (b) (4) bags, and $15.2 (b) (4) \times 12.7 (b) (4)$ for (b) (4) bags) must conform to the technical drawing of the freezing bag. Incoming primary packaging material testing is based on c(b) (4) testing for endotoxin and (b) (4) as described in (b) (4) of the bag materials (EVA and EVA/PVC) are compared against reference standards.

Reviewer comment: Additional information regarding bag AQLs was provided in Amendment 17 (response to CMC IR of 07/09/2021, received 07/19/2021) and has been incorporated above. For each lot received (b) (4) bags, (b) (4) bags are pulled for visual inspection. This amendment also describes the reference standards for (b) (4) comparison, which were created from bags, ports, and fill

tubes from a sample bag. The (b) (4) numbers are used to identify the resins used (EVA and PVC). This is acceptable.

Container closure system quality management

A Quality Management System (QMS) encompassing manufacturing and quality activity associated with processing of the DP and cryobag has been developed, outlining the applicant's approach to compliance with 21 CFR 210, 211, and 820. This QMS includes the following elements summarized below:

- *Design Controls (per 21 CFR 820.30)*: A design and development plan (including user requirements, technical design requirements, design verification, and design validation) and a device master record (including all required tests and procedures for production) have been established for the DP and freezing bag.
- *Management Responsibility (per 21 CFR 820.20)*: Established procedures and practices to ensure appropriate management oversight are in place, including review of quality data to ensure suitability and effectiveness of the quality system, adequate resources are provided for operations, and an adequate organization structure is maintained.
- *Purchasing Controls (per 21 CFR 820.50)*: Purchasing controls are in place to ensure that all materials conform to specified requirements, including supplier qualification and monitoring via audits and inspections, QC verification of incoming material via COA/COC verification, and internal testing according to pre-defined quality standards. Incoming materials and components are only available for manufacturing use after they have been released by the quality unit.
- *Corrective and Preventative Actions (per 21 CFR 820.100)*: Defined CAPA procedures are in place, including issue identification and assessment, investigation and assessment of root cause, identification and implementation of corrective and preventative actions (including evaluation and verification of effectiveness), records review, approval, and timely closure, and management review of the overall CAPA process.

A risk management plan has been developed to identify, evaluate, and control risks during preparation and shipping of the DP and freezing bag. The primary container closure is a 510(k) cleared Class II medical device intended for the storage and delivery of blood components. It has been verified and validated for safety and effectiveness by the manufacturer, as documented in their design history file. The filled cryobags will be contained within a secondary packaging system (aluminum cryocassette) to protect from damage during storage and transportation, and shipping and transportation validation studies have been conducted to ensure product safety and integrity. In addition, Janssen will conduct a site audit for each DP administration site, which will include training site personnel in product handling and administration according the prescribing information and universal precautions (for bloodborne pathogens). Control measures and/or mitigations for identified risks have been incorporated into the manufacturing, preparation, and administration process. The overall risk analysis concludes that there is a low likelihood of container closure system related safety risks for patients, and the benefits for patients outweigh these risks.

Shipping system

The shipping system used to transport the final cryopreserved DP from the manufacturing site to administration sites is a (b) (4) liquid nitrogen dry shipper consisting of porous material surrounding a vacuum flask (containing a removable rack) with a removable "smart cap" lid containing a temperature indicator button and a multi-functional (b) (4) data logger. The dry shipper containing the DP is loaded into a protective outer pack (31" x 14.5" x 14.5") with a dolly. The dry shipper is charged by (b) (4) and the shipper is ready for use. These steps are performed by the courier. At the manufacturing site, the warehouse team confirms temperature of the cryoshipper and ensures that the provided security seal and DP shipping waybill match. The DP is verified via COI/COC procedures, sealed in containment

packaging, and loaded into the cryoshipper rack along with dunnage. The security seal is applied, and the rack is loaded back into the cryoshipper. The lid is then replaced and a second seal is attached to the lid. Real-time temperature monitoring during shipment is performed via the on-board (b) (4) recorder, which uses an integrated probe positioned immediately above the DP/rack payload. The (b) (4) recorder has cellular-tracking and data logging functions and can monitor multiple parameters including location, environmental conditions, and motion.

On receipt at the administration site, the security seal number and cryoshipper serial number are confirmed to match the waybill and the cryoshipper temperature is checked. The lid and rack are then removed and DP is removed from the containment packaging and placed into storage per administration site procedures. A product receipt checklist is completed to document product and shipper condition on arrival, and this is submitted to Janssen for record.

Reviewer comment: Descriptions of the shipping system and packout/unpack procedures were provided in Amendment 17 (response to CMC IR of 07/09/2021, received 07/19/2021) and are acceptable.

Overall Reviewer's Assessment of Section 3.2.P.7:

Container closure and shipper information is acceptable. In the BLA OS, the applicant self-identified the DP and (b) (4) bag as a combination product, citing FDA guidance (Container Closure Systems for Packaging Human Drugs and Biologics – Guidance for Industry, July 1999), with the rationale that this is a combination product as the freezing bag will be used to contain and deliver the cryopreserved DP. As such, compliance with the required Quality Systems Regulations (QSRs) applicable to combination products was described in detail in the submission. However, following internal discussions with OTAT management and precedent from other approved CAR T cell products, it was decided that this would be reviewed as a conventional container closure system rather than as a combination product. Information to clarify minor details was requested during the review cycle and responses were acceptable, as outlined above. There are no other concerns or outstanding deficiencies regarding container closures.

3.2.P.8 Stability

Reviewed by MC

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

Long term stability studies at $\leq -120^{\circ}\text{C}$ to support the proposed shelf life of 9 months have been completed for development batches manufactured at (b) (4) and (b) (4). Studies on process validation (PPQ) and commercial batches are ongoing and 6 months study results have been provided. Accelerated study using healthy donor lots stored at (b) (4) has been completed. In use stability studies assessing thawed material held at room temperature have also been completed.

Long-term stability study:

Long term stability study was conducted using developmental, process validation and commercial batches. Except for batch (b) (4), which was manufactured using patient apheresis material and was manufactured at (b) (4) using the representative (b) (4) process, all other developmental batches, which includes (b) (4) Stability Runs (b) (4), were manufactured using healthy donor apheresis material and manufactured using the clinical representative (b) (4) manufacturing process. All the PPQ batches were manufactured using patient apheresis material and were manufactured at a target dose of 0.75×10^6 viable T cells/kg. Stability of all lots was tested in (b) (4) DP container closure. A comparative study demonstrated that all drug product quality attributes from (b) (4) bag are equivalent to that of (b) (4) bag. Commercial stability batches were manufactured using both healthy donor and patient apheresis material. Table 90 is showing the test parameters and acceptance criteria used for developmental batches.

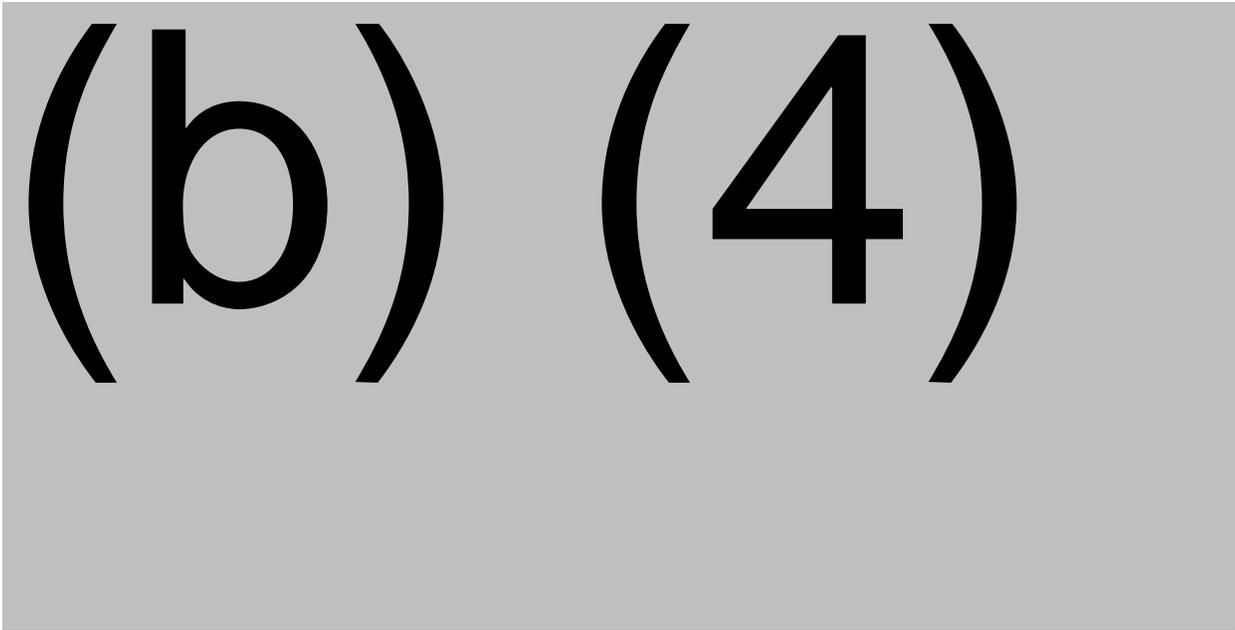
Table 90: Test Parameters and Acceptance Criteria for Long-term Stability Studies

Parameter ^a	Protocol acceptance criteria ^a
(b) (4) viability	(b) (4)
Phenotype (b) (4) Purity	
Viable CAR ⁺ T Cells Concentration (b) (4)	
(b) (4)	
CAR Expression	
Sterility	No growth
Appearance of Primary Container	Each bag is without visible defects or leaks
Appearance of Color	(b) (4)
(b) (4) viability (%) ^b	Report results
(b) (4)	(b) (4)

^a Test parameters and acceptance criteria used in temperature excursion study

^b Test parameters were excluded for (b) (4) batches

All developmental, PPQ and commercial lots met all appearance criteria at all time points. Sterility testing passed at all time points. No leakage of bags was observed. Appearance of color remained the same. Viable cell concentration and Total CAR⁺ viable T cells in the final container were within acceptable ranges. Viability ranged between (b) (4) with no evidence of a trend through the time points that were being tested. CAR expression and (b) (4) were within acceptance ranges for all lots at all time points tested. Some variability was seen for these parameters, but no apparent trends were observed. Viability, % CAR expression, and (b) (4) test results of developmental batches and PPQ and commercial batches are shown in Figure 18 and Figure 19, respectively.



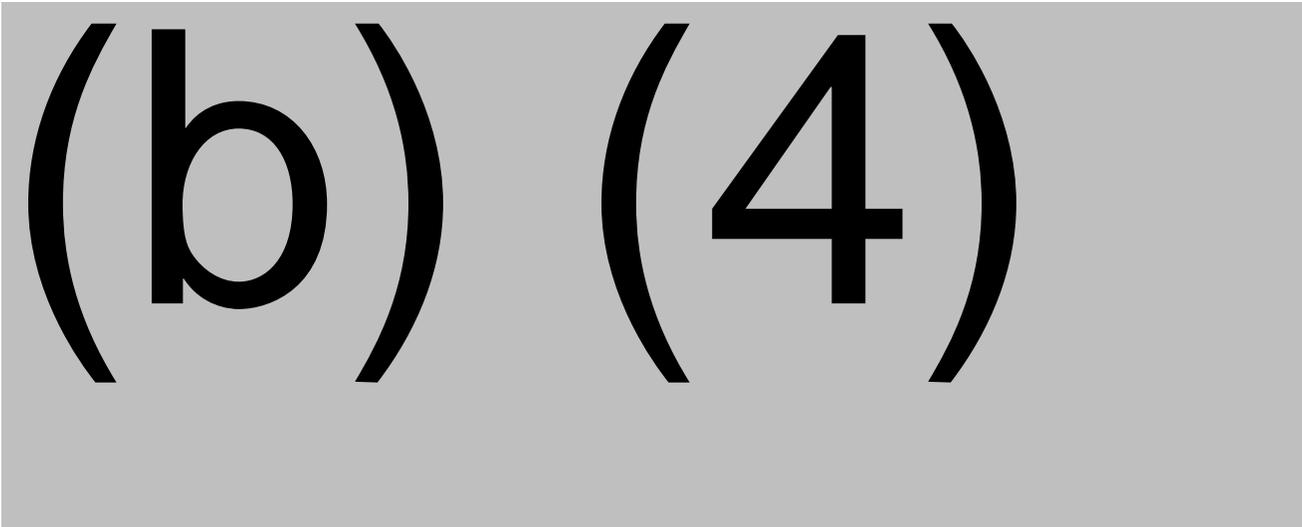


Figure 18 and 19: Upper and Lower panels are showing trend plots of (b) (4) viability, CAR expression and (b) (4) over the time of storage. Acceptance criteria for PPQ and commercial batches were established based on T=0 data (initial) which was leveraged from release testing. A comparative analysis demonstrated that the T=0 samples, which are stored in a (b) (4), are equivalent to all other stability samples stored in freezer bags.

Reviewer comment: Janssen proposes a DP shelf life of 9 months at $\leq -120^{\circ}\text{C}$ based on the 9 months stability data available for the developmental lots (b) (4) stability run and (b) (4). Additionally, Janssen provided 6 months stability data for PPQ and commercial batches and committed to continue the study for additional 3 months. The long-term stability study test results of all test parameters for both developmental and commercial batches were within acceptance criteria. Sterility was maintained for all lots for time points tested. No leakage of bags and no change in appearance of color were observed. For some lots, variability is seen in viability, %CAR expression and (b) (4), however, no apparent trends were observed in these test parameters. Janssen expects that that this trend will be maintained for additional 3 months for PPQ and commercial batches and commits to provide data for these batches when they are available. The proposed shelf-life of 9 months under long term storage conditions ($\leq -120^{\circ}\text{C}$) is acceptable.

Temperature excursion or accelerated stability studies: A temperature excursion study was conducted over 6 months using development batch (b) (4) and commercial batches (b) (4) using healthy donor apheresis material. Stability of the DP was tested using low and high concentrations of target cells in 30 mL (b) (4) bag. The cryopreserved DP bags were held at $< -120^{\circ}\text{C}$ for up to (b) (4) days prior to exposure to accelerated temperature of (b) (4). After exposure to (b) (4) for (b) (4), the bags were tested immediately and placed for long-term stability at $\leq -120^{\circ}\text{C}$ until testing at 1 and 6 months. For the commercial batches, testing was expanded to 9 months. For these batches, the cryopreserved DP bag held at $< -120^{\circ}\text{C}$ for (b) (4) prior to exposure to accelerated temperature of (b) (4). For these batches, up to 3 months data have been provided. Test parameters and acceptance criteria are in Table 90.

Reviewer comment: All test parameters met protocol acceptance criteria when stored at (b) (4) for (b) (4) and later at $\leq -120^{\circ}\text{C}$ for one and six months except for sterility for batch (b) (4) at high concentration. Sterility was failed at T=0 ((b) (4)) and T=6 months. Since sterility testing was passed at (b) (4) at high concentration and passed at all time points in low concentration, according to Janssen, the positive test results were likely due to an isolated contamination event, which was caused by two skin bacteria, hence, attributed to the operators, and not due to contamination of the harvest itself. The data are supportive, fluctuation in some quality attributes did not affect the overall stability.

In-use stability study:

In-use stability study was conducted on DP bags (30 mL fill volume in a (b) (4) bag) from (b) (4) process validations runs using (b) (4) patient and (b) (4) apheresis materials. Samples from each donor were tested (b) (4). One sample represents in-process hold times for the commercial process (control) and the other represents stressed condition in which the sample was tested with extended-cumulative hold times (cumulative hold). All samples were evaluated immediately at T0 post thaw, T1.5h post thaw, T2.5h post thaw and (b) (4) post thaw at ambient temperature (b) (4). The test parameters and acceptance criteria for in-use stability study are shown in Table 91.

Table 91: Test parameters and acceptance criteria for in-use stability study

Test parameters	Protocol acceptance criteria
Viability (%)	(b) (4)
Viable Cell (b) (4) (x10 ⁶ cells/ mL)	(b) (4)
CAR Expression (%)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	Report Results
Appearance of Color ²	(b) (4)
Appearance of Primary Container ^b	No Visible Defects or Leaks
Appearance of Particulate Matter ^b	Free of Visible Foreign Particulates
^a characterization assay for information only. ^b Test methods used to examine color, appearance of primary container, and particulate matter were performed only at T0. Visual inspection was used as the test method to examine these quality attributes.	

The results are provided for (b) (4) batches. Results from batch (b) (4), patient (b) (4), control condition had a DP OOS ((b) (4)) and was excluded from the study. However, the corresponding cumulative hold sample from the same donor, (b) (4), was evaluated. All samples, control, and cumulative hold, from each donor, healthy and patient, remained within protocol acceptance criteria post-thaw for up to (b) (4) hours in room temperature. Each DP bag passed all visual inspection tests immediately post thaw as well. CAR-T specific (b) (4) was observed for all batches tested using both the commercial release assay as well as the characterization method. The characterization test results for both control and cumulative hold conditions showed a decreasing trend in (b) (4) over the study hold time ((b) (4)), which is significant). A decreasing trend in viability was also observed, however, viability remained above (b) (4) for all conditions for up to (b) (4) hours post-thaw. A decreased trend was also observed in CAR expression.

Reviewer comment: Although a decreasing trend was observed for some quality attributes, all samples remained within release acceptance criteria post-thaw for up to (b) (4) hours. Overall, the data suggest that the product is stable up to (b) (4) hrs. post thaw in room temperature. According to the prescribing information, cilta-cel DP should be administered to patient within 2.5 hrs post-thaw.

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

Janssen will continue to collect DP stability data on the development DP Batch (b) (4), (b) (4) PPQ batches ((b) (4)), and (b) (4) commercial stability batches ((b) (4)), through 9 months (the currently proposed DP shelf life) and up to (b) (4) months at -120 (b) (4) °C. The test parameters include Appearance of Color, Sterility, (b) (4) Viability, Viable Cell Concentration, total CAR⁺ viable T cells, CAR Expression and (b) (4). The tests will be performed based on methods and specifications provided in 3.2.P.5.2 Analytical Procedures and 3.2.P.5.1 Specifications, respectively.

Reviewer comment: The post approval stability protocol provided in Amendment 56 (to replace (b) (4) with (b) (4) assay; received on 10/14/2021) is acceptable except that it does not address the issue of lacking (b) (4) results in currently available stability data. There is no (b) (4) data for any of the ongoing lots at T0, so it would not be feasible to analyze its trend in the ongoing study. Although the provided data, including potency-related measures (%CAR expression and (b) (4)), support the proposed shelf life, the change of potency assay is a major change in DP release and stability testing. Therefore, additional data should be collected through post-approval studies to demonstrate DP stability using the new potency assay. In Amendment 64 (received on 11/15/2021, in response to IR #49 sent on 11/10/2021), the applicant agreed to place additional 3 DP lots on stability protocol to collect (b) (4) data in long-term storage. This is acceptable.

Overall Reviewer's Assessment of Section 3.2.P.8:

- The stability data from development lot, process validation lots and stability lots support the proposed 9 months long-term storage shelf-life for cilta-cel DP. The data also support a post-thaw stability of up to (b) (4) hours at ambient temperature, however DP administration instructions will indicate that the DP should be administered within 2.5 hours.
- Data submitted in the original submission and in Amendment 5 (30-day stability data update as agreed upon in pre-BLA meeting; received 04/30/2021) was not sufficient to support the proposed long-term shelf-life. In response to IR #18 (07/27/2021) and IR #45 (10/15/2021), Janssen provided additional stability data updates in Amendment 29 (received 08/05/2021) and Amendment 58 (received 10/20/2021), which support the proposed shelf-life.
- The post-approval stability protocol and stability commitment are acceptable.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by GEP

Janssen's manufacturing facilities and equipment were reviewed by DMPQ (see DMPQ review memos for details). In summary, due to travel restrictions, the (b) (4) LVV manufacturing facility was reviewed by DMPQ and DCGT via a Section 704(a)(4) records review request in lieu of an on-site inspection. Based on this records review, the facility appears acceptable for the manufacture of LVV. An on-site pre-license inspection of the Janssen (b) (4) CAR T cell manufacturing facility was conducted by DMPQ, DCGT, and OBPO (b) (4), with no objectionable conditions observed and no Form 483 issued (see EIR for details). This facility is acceptable for DP manufacture.

3.2.A.2 Adventitious Agents Safety Evaluation

Reviewed by MC

Cilta-cel is an autologous gene modified cellular product, hence the use of traditional sterilization and virus clearance methods do not apply. To ensure product safety, multiple control strategies were employed to minimize the adventitious agent contamination in the (b) (4) vector and cilta-cel. These strategies include qualification of raw materials through raw material sourcing and testing, environmental controls during vector and Cilta-cel manufacturing, and vector and cilta-cel release testing, which include tests for sterility, endotoxin and mycoplasma.

3.2.A.2.2 Control of Adventitious Agents in the production of the (b) (4) vector

Raw material qualification by supporting documents, which include COAs, COOs and MFs, and testing performed by Janssen are documented in Table 3 and Table 4. Additional information on raw materials sourcing and testing, which includes information on adventitious agent testing and viral inactivation procedures for some key materials, is discussed below.

(b) (4)

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Reviewer comment: Due to the nature of LV, which is an enveloped virus, viral inactivation, or removal in the LVV manufacturing process was not feasible. Therefore, the control of the adventitious agents depends on the control of animal and human derived raw materials. Materials of animal origin are sourced from countries with reduced TSE risk for LV manufacturing and materials of human origin have documented donor eligibility testing and screening in accordance with FDA requirements. Overall, the presented control measures are adequate. The risk of adventitious agent contamination in LVV is nominal.

3.2.A.2.3: Control of Adventitious Agents in the production of Cilta cel

Since the apheresis material is autologous in nature, any viruses present in the material would be patient-derived, therefore, the material will pose a low risk to the patients in terms of adventitious agents. The supporting documents and testing methods used to qualify the raw materials are in Table

41 and Table 42. Additional information on the control of raw materials through sourcing and testing is discussed below.

(b) (4)

[Redacted text block]

(b) (4)

Reviewer comment: Media and reagents used in cilta-cel manufacture were sourced from qualified vendors. Materials of human origin have documented donor eligibility testing and screening in accordance with FDA requirements. When applicable, FDA approved products are used (e.g., (b) (4)). Manufacturing steps used for viral clearance were efficient in reducing the viral burden in key raw materials. Overall, the presented control measures are adequate.

❑ **Viral Clearance Studies**

Viral clearance studies were not performed on the Lentiviral vector (LVV) or the DP. However, studies on residual LVV impurity clearance during the DP manufacturing process was conducted and found acceptable (LVV 3.2.S.2.6 Manufacturing Process Development, 3.2.S.3.2 Impurities).

Overall Reviewer’s Assessment of Section 3.2.A.2:

- ❑ Overall, the measures for controlling the presence of adventitious agents are acceptable as submitted. The lentiviral virus is below the limit of detection in the final DP and replication competent virus has not been detected to date. There are no concerns.

3.2.A.3 Novel Excipients

Not applicable – no new excipients are used.

3.2.R Regional Information (USA)

❑ **Executed Batch Records**

Reviewed by ZY

The commercial representative batch record TV-MBR-14493 (Version: 2.0 Effective Date: 26 Jan 2021) is provided. The executed batch records for the DP manufacturing process validation lot# (b) (4) were provided and reviewed in (b) (4) sections covering the entire manufacturing stage:

(b) (4)

- Harvest – Day (b) (4)
- Wash and Formulation Calculation – Day (b) (4)
- Formulation and Filling – Day (b) (4)
- Cryopreservation of Cells – D (b) (4)

No issues identified. Additional batch records review was conducted during the (b) (4) facility inspection. See the EIR report for additional details.

❑ **Method Validation Package**

Method validation packages are provided and reviewed in 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures, and 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.

❑ **Combination Products**

Not applicable. This is not a combination product (see 3.2.P.7 Container Closure System).

❑ **Comparability Protocols**

Reviewed by ZY

(b) (4) comparability protocols (CPs) were submitted, including one for LVV manufacturing (b) (4) increase, and (b) (4) analytical method transfer protocols.

(b) (4)

[Redacted text block]

Analytical method transfer proposals

- (b) (4) of the CPs concern assay validation at Janssen sites of LVV release testing methods (i.e., (b) (4)) that are currently contracted to (b) (4)). The purposes of these CPs are to demonstrate that QC laboratories existing within the Janssen network may be qualified to perform these tests.
- In each of the other (b) (4) CPs, Janssen proposes to transfer a current, validated, method from the approved QC release laboratory to other Janssen laboratories to supplement the sites qualified for performing release testing of the LVV and DP. These include (b) (4)

All of the test methods were initially developed at Janssen's (b) (4) (i.e., (b) (4) R&D Lab). For those tests that are currently conducted by (b) (4), the new Janssen methods have gone through platform validation at (b) (4) R&D. Co-validations between the (b) (4) R&D laboratory and

the laboratory the assay will be transferred to for routine testing will be conducted using (b) (4) LVV materials. For those tests that are currently performed at Janssen, (b) (4) R&D Laboratory will also serve as the reference lab for each co-validation. Validation protocols described in the CPs are acceptable, and generally include specificity, precision (repeatability and intermediate precision), limit of quantification (LOQ), accuracy, linearity, range, and sample stability. Bridging studies will also be conducted for the tests that are currently performed at (b) (4), to determine assay equivalency and the need to establish new acceptance criteria.

Following approval of the CPs, Janssen proposed to provide the comparability/validation data generated in accordance with the CP in the subsequent annual report, unless there are changes to acceptance criteria, in which case the change will be submitted as CBE-30.

Reviewer comment: *Janssen clarified in Amendment 57 (received 10/14/2021) upon request through IR #41, that the (b) (4) Lab will serve as the reference lab for all the co-validations.*

Although the provided assay validation protocols are acceptable, impact of these changes on release specification acceptance criteria is currently unclear. Acceptability of the statistical approaches used to determine the number of batches required for bridging studies, as well as the post-change acceptance criteria will need to be determined upon reviewing the data. Therefore, the applicant was informed in IR #48 that these proposed analytical method changes should be submitted as supplements to the BLA. In Amendment 65 (received 11/05/2021), Janssen proposed that addition of a testing laboratory for release or stability testing within an existing location in the approved BLA will be reported as a CBE-30. This is acceptable.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Reviewed by GEP

Janssen claims a categorical exclusion from the need to prepare an environmental assessment (EA) under 21 CFR 25.31(c). Janssen states that they are not aware of any extraordinary circumstances that would require the preparation of an EA. Cilta-cel consists of human cells transduced with a non-replicating LVV. These cells are unable to survive outside the human body and are degraded into naturally occurring substances in the environment.

Reviewer comment: *Categorical exclusion under CFR 25.31(c) is acceptable. There is no need to prepare a Finding Of No Significant Impact (FONSI).*

B. Labeling Review

Reviewed by ZY

Full Prescribing Information (PI):

The following sections of the PI were reviewed: Section 2 (Dose and Administration), Section 3 (Dosage Forms and Strengths), Section 11 (Description), Section 12 (Clinical Pharmacology – Mechanism of Action) and Section 16 (How supplied / storage and handling). Description of cilta-cel dosage form and mechanism of action is consistent with other sections in the BLA. Procedures for receipt and preparation of cilta-cel at clinical site are described in sufficient details and are acceptable.

Reviewer comment: *In the original PI, it was not clearly described where the DP bag and cassette will be stored after receipt at the clinical site. IR #33 was sent requesting a protocol for DP handling if the patient is not expected to be ready for administration before the shipping container expires. In Amendment 48 (received 9/21/2021), Janssen clarified that qualification of a clinical site is contingent*

on having dedicated LN2 storage, including a back-up freezer in the event of a failure. A Receipt and Storage Manual (Version 2; dated June 2021) was provided in the amendment, which states that DP must be placed in local site LN2 storage immediately following unpacking from the shipper and verification of CoC/Col. This is acceptable.

Carton and Container Label:

Figure 20. Example of cilta-cel infusion bag label (70 mL suspension)

ciltacabtagene autoleucl
CARVYKTI™
Suspension for Intravenous Infusion

Dose: One sterile bag for infusion.
Contents: A maximum of 1×10^8 CAR-positive viable T cells in a 70 mL frozen suspension per patient-specific infusion bag, containing 5% DMSO.

FOR AUTOLOGOUS USE ONLY. **FOR INTRAVENOUS USE ONLY.**

Dosage: See Prescribing Information.
Storage: Store and transport in a vapor phase of liquid nitrogen $\leq -120^\circ\text{C}$ (-184°F). Thaw before using.
DO NOT re-freeze or refrigerate once thawed.
DO NOT irradiate.
DO NOT use a leukodepleting filter.
 CULTURED, GENETICALLY MODIFIED.
 NO U.S. STANDARD OF POTENCY.
 NOT EVALUATED FOR INFECTIOUS SUBSTANCES.
NO PRESERVATIVE
Attention: Dispense the enclosed Medication Guide to each patient.
Rx only
One Sterile Bag for Infusion
Mfg. by: Janssen Biotech, Inc., Horsham, PA 19044
 U.S. License No. 1864

Upon receipt: Match the identity of the patient with the patient identifiers on the cassette and infusion bag.

BAG ID: COI [followed by Bag Number]
 LOT: XXXXXXXX EXP: YYYY-MMM-DD
 ORDER ID:
 PATIENT NAME:
 DOB: YYYY-MMM-DD
 MEDICAL RECORD NO.:

DIN: 0100000000000000

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LEGEND BIOTECH janssen

- The labels for 30 mL fill bag and cassette have a different NDC (57894-111-02) than the example shown in Figure20.
- The volume of cell suspension (i.e., 30 mL or 70 mL) is indicated in the field “Contents” and matches with the NDC.
- The only difference in the cassette label is the statement beneath “Rx only”: “One Metal Cassette Containing One Individually-Packed Infusion Bag”.

Reviewer comment: The initial labels provided complied with 21 CFR 610.60-62 except:

- The same NDC (57894-111-01) for 30 mL and 70 mL fills (a separate NDC is needed for each fill size)

- *Contains “Manufactured with (b) (4)” without calculated amount (per 21 CFR 610.61). (b) (4) is used only during (b) (4) production, and is not a reagent in either LVV or DP manufacturing. The probability of a DP lot to have sufficient amount of (b) (4) to cause hypersensitivities is negligible. This statement is therefore not necessary.*

IR #49 was sent to Janssen on 11/10/2021 requesting the applicant to address this issue. Updated labels were provided in Amendment 64 (received on 11/15/2021). Janssen removed the (b) (4) statement but requested to use a single NDC for cilta-cel. Janssen’s position was that cilta-cel is administered as a single use dose; the container size is not the relevant factor in determining what material should be administered to a patient. In addition, Janssen stated that multiple NDCs for product differentiation would jeopardize maintaining the data integrity of this supply chain process, as NDC is used in product tracking (i.e., at the time of prescribing doctor’s order) before the bag size is determined. Based on consultation with OCBQ Associate Director for Policy and CBER IOD, it was determined that two NDCs for the different bags and volumes are needed in order to maintain federal regulatory requirements and consistency across products. Janssen was notified of this decision by email on 12/02/2021, with a reference to 21 CFR 207.33. In Amendment 68 (received on 12/17/2021), Janssen updated the infusion bag and cassette labels as requested. The human-readable format portion of the NDC was further updated in Amendment 73 (received on 01/24/2022, in response to FDA recommendation in IR # 55, sent on 01/18/2022) to follow the 3-segment format that identified the labeler, product and trade package size.

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Reviewed by GEP

Primary objectives of the 68284528MMY2001 (CARTITUDE-1) study were characterization of the safety and evaluating the efficacy of cilta-cel. Determination of minimal residual disease status was an efficacy evaluation performed using the clonoSEQ[®] assay to define myeloma clones in bone marrow aspirates collected at baseline and post-treatment; an assay description and summary of validation is provided below. Secondary objectives included characterization of the pharmacokinetics and pharmacodynamics (PK/PD), assessment of immunogenicity, and further characterization of the efficacy of cilta-cel. Blood and serum samples were collected for assessment of cilta-cel pharmacokinetics, immunogenicity (antibodies to cilta-cel), and predictive biomarkers of response or resistance to cilta-cel. These samples were assessed by various methods, including flow cytometry, (b) (4), immunoassay, and (b) (4), with analytical method qualification and/or validation data summarized in module 5.3.1.4 as follows:

□ clonoSEQ[®] Minimal Residual Disease Assay

This is a diagnostic/monitoring assay to determine minimal residual disease (MRD) status in BCMA-CAR T cell treated patients, a key clinical response measurement. The clonoSEQ assay uses multiplexed PCR and next-generation sequencing (NGS) using the Illumina NextSeq 500/550 platform to identify and quantitate rearranged IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences and translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in bone marrow to monitor changes in tumor burden. The frequency and distribution of clonal sequences associated with the malignant lymphocyte population determines the measurable number of cancer cells in the patient during and after treatment. This assay is applicable to multiple forms of B cell malignancy (acute lymphoblastic leukemia [ALL], chronic lymphocytic leukemia [CLL], and multiple myeloma [MM]). The basic assay design is to extract gDNA and amplify target sequences and housekeeping genes using primers containing barcoded sequences to create a library that is then sequenced. Sequence data is processed using a proprietary algorithm to remove amplification bias and the immune repertoire of barcoded sequences is assessed for the presence of dominant clones. Sequences are compared against a B cell repertoire database

and assigned a uniqueness value along with an abundance relative to other sequences. For MRD assessment, the sequence repertoire after treatment is re-assessed against baseline (pre-treatment) results and previously identified dominant clones are detected and quantitated to determine the MRD level. MRD is reported as a frequency that quantifies the level of residual disease based on the number of remaining copies of initially dominant sequences relative of the total number of nucleated cells in the sample.

The assay was performed and validated at (b) (4)

Validation studies used (b) (4)



Reviewer comment: The extensive validation document provided indicates that the clonoSEQ assay is validated and able to reliably detect MRD in clinical MM bone marrow samples. There are no CMC concerns regarding use of this assay to determine patient MRD negative status.

- **Flow cytometry assay to measure BCMA CAR T cells ((b) (4))**
This method is a (b) (4) developed at (b) (4) to measure BCMA-specific CAR T cells in human peripheral blood and bone marrow collected in sodium-heparin tubes. Assay validation is described in the document *RPT-10012: Flow Cytometry*

assay to measure JNJ-68284528 BCMA CAR-T cells in human peripheral blood and bone marrow. In summary, CAR positivity was determined by staining with (b) (4)

[Redacted]

Reviewer comment: Pre-defined assay validation acceptance criteria were met for this assay, indicating that it is appropriately validated for enumeration of T cells expressing BCMA in patient blood and bone marrow samples.

□ **Flow cytometry assay to measure BCMA CAR T cells ((b) (4))**

This is a flow cytometry method developed to quantitate JNJ-68284528 BCMA-specific CAR T cells in (b) (4)

[Redacted]

Reviewer comment: This assay is acceptably validated and was used for PK studies. There are no concerns.

□ **Flow cytometry assay for BCMA expression on bone marrow plasma cells**

This was a flow cytometry assay for exploratory purposes to assess BCMA expression on plasma cells from BMA samples. The assay was developed at (b) (4)

[Redacted]

(b) (4)



Reviewer comment: This assay is intended for exploratory purposes only. The intra-instrument variability was high and cell clumping (a common problem with poorly prepared samples) may have contributed to this. Note that the sample matrix is BMA, rather than blood, which presents some sample preparation challenges. Ultimately, this assay may be considered qualified rather than validated, which is acceptable for exploratory analyses.

□ (b) (4) **assay for absolute quantitation of CAR T cells**

This method is a (b) (4) assay using a CAR-specific (b) (4)



(b) (4)



Reviewer comment: A full assay description, including system suitability controls is provided, along with extensive validation information. There are no concerns with (b) (4) assay validation or performance.

□ **Soluble BCMA assay**

(b) (4)



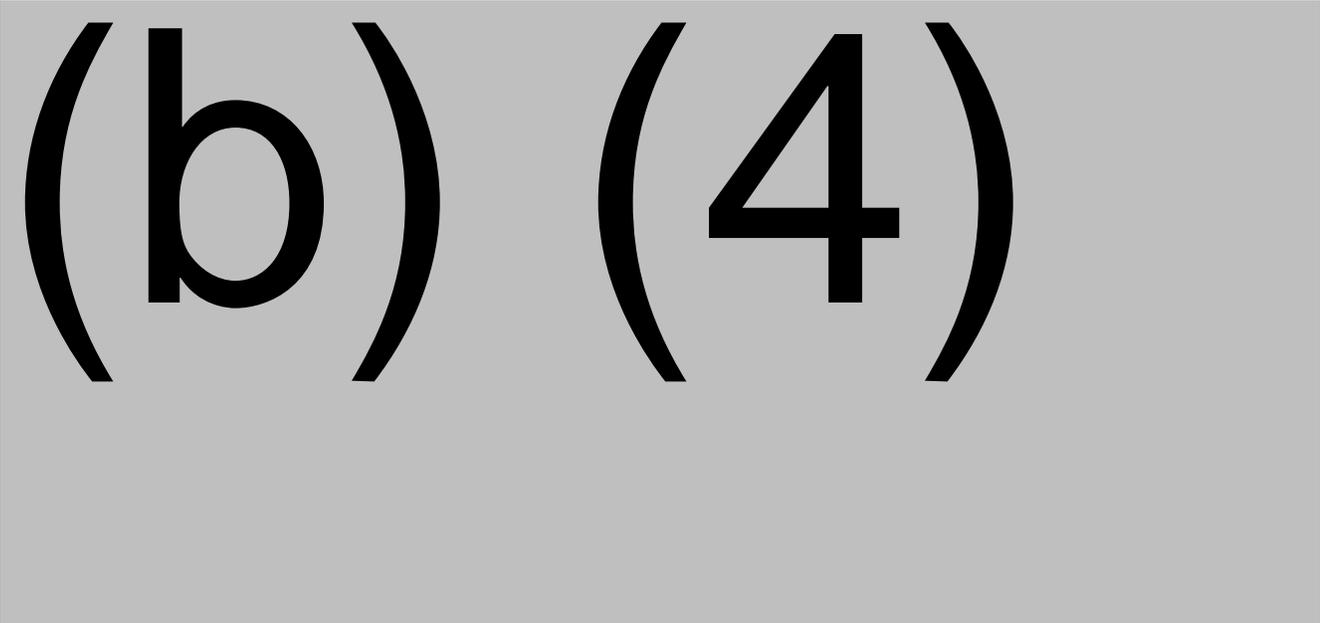
accuracy and precision were met. (b) (4) All pre-defined acceptance criteria for



Reviewer comment: *This assay and assay validation is acceptable.*

□ **Cytokine assays**

Cytokine levels in human serum were assessed at (b) (4) assays. These assays and validated for precision and accuracy, assay range (LLOQ, ULOQ, and limit of blank [(b) (4)]), selectivity/spike recovery ((b) (4)), (b) (4) linearity, range, and sample stability. Selectivity, precision, (b) (4)) between replicate samples. Specificity was assessed using (b) (4). Assay ranges and reference ranges (based on 95% cut-offs from (b) (4) lots of normal serum, where performed) for each analyte are shown in Table 93.



Reviewer comment: *These cytokine assays are for clinical monitoring (PK study) purposes. Note that the MSD assays have a much wider linear range than conventional (b) (4) methods and are also validated by the manufacturer. The validation reported here is in addition to the manufacturer's validation and is acceptable.*

□ (b) (4)

[Redacted content]

(b) (4)

[Redacted text block]

□ **Replication Competent Lentivirus (RCL) monitoring assay**

(b) (4)

[Redacted text block]

Assay qualification was otherwise unremarkable.

Reviewer comment: This assay was used as a safety monitoring assay for evidence of RCL in patient PBMC samples. While the wider system suitability acceptance criteria for the (b) (4) standards might impact accurate quantitation of (b) (4) (by affecting the accuracy of the standard curve), it will not affect the ability of the assay to qualitatively detect (b) (4) in patient samples. The assay is thus fit for purpose and is qualified (but not validated) for use.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

Assays used to support secondary study endpoints and for clinical monitoring are adequately described and either validated or qualified and fit for purpose. There are no concerns with diagnostic or PLK/PD assay methods.