

CBER CMC BLA Review Memorandum

BLA STN 125714

**lisocabtagene maraleucel
BREYANZI**

Reviewers:

Nirjal Bhattarai, Ph.D. OTAT/DCGT/GTIB
Tiffany Lucas, Ph.D. OTAT/DCGT/GTB
Kimberly LW Schultz, Ph.D. OTAT/DCGT/GTB

1. **BLA#:** STN 125714

2. **APPLICANT NAME AND LICENSE NUMBER**

Juno Therapeutics, Inc.
400 Dexter Avenue N. Suite 1200
Seattle, WA 98109

3. **PRODUCT NAME/PRODUCT TYPE**

Non-proprietary/Proper/USAN: lisocabtagene maraleucel
Proprietary name: BREYANZI
Company Code: JCAR017
UNII Code: 7K2YOJ14X0
NDC Codes: Outer box: NDC 73153-900-01
CD8 DP component: NDC 73153-901-08
CD4 DP component: NDC 73153-902-04

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

Pharmacological Category: CD19-directed genetically modified autologous T cell immunotherapy
Dosage Form: Cell Suspension for Infusion
Strength/Potency: 50-110 x 10⁶ CAR-positive viable T cells
Route of Administration: Intravenous Infusion
Indication: For treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least two or more lines of systemic therapy.

5. **MAJOR MILESTONES**

BB-IND-16506 Initial IND submission:	29MAY2015
BB-IND-16506 Orphan drug designation:	
Diffuse large B-cell lymphoma (DLBCL)	27APR2016
Follicular lymphoma (FL)	07SEP2017
Primary mediastinal B-cell lymphoma (PMBCL)	12JUL2018
BB-IND-16506 Breakthrough Therapy Designation for r/r NHL, DLBCL, and PMBCL:	15DEC2016
Regenerative Medicine Advanced Therapy Designation:	
r/r NHL, DLBCL, and PMBCL	20OCT2017
r/r CLL and SLL	05MAR2019
r/r large B-cell lymphoma	17AUG2020
BB-IND-16506 Pre-BLA type B meeting:	05AUG2019
BLA 125714 received:	18DEC2019
BLA 125714 filed:	12FEB2020
BLA 125714 mid-cycle meeting:	31MAR2020
BLA 125714 Major Amendment Acknowledgement	05MAY2020
BLA 125714 late-cycle meeting:	02SEP2020
BLA 125714 PDUFA action date:	16NOV2020

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Kimberly LW Schultz, Ph.D OTAT/DCGT/GTB	3.2.S Drug Substance: (b) (4) (Lentiviral vector) Sections: 3.2.S.1, 3.2.S.2.2, 3.2.S.2.5, 3.2.S.2.6, 3.2.S.3.1, 3.2.S.6 3.2.S Drug Substance: (b) (4) Component Sections: 3.2.S.1, 3.2.S.2.1, 3.2.S.2.2, 3.2.S.2.5, 3.2.S.2.6, 3.2.S.3.2 3.2.P Drug Product: CD4 or CD8 Component Sections: 3.2.P.1, 3.2.P.2, 3.2.P.3, 3.2.S.7 Appendices: 3.2.A.1, 3.2.A.2 Module 1 A (Environmental Assessment) and B (Labeling)
Tiffany Lucas, Ph.D OTAT/DCGT/GTB	3.2.S Drug Substance: (b) (4) (Lentiviral vector) Sections: 3.2.S.2.1, 3.2.S.2.3, 3.2.S.2.4, 3.2.S.3.2, 3.2.S.4, 3.2.S.5, 3.2.S.8
Nirjal Bhattarai, Ph.D OTAT/DCGT/GTIB	3.2.S Drug Substance: (b) (4) Component Sections: 3.2.S.2.3, 3.2.S.2.4, 3.2.S.3.1, 3.2.S.4, 3.2.S.5, 3.2.S.6, 3.2.S.7, 3.2.P Drug Product: CD4 or CD8 Component Sections: 3.2.P.4, 3.2.P.5, 3.2.P.6, 3.2.P.7, Modules 4 and 5 (Analytical Procedures and Assay Validation)
Steven Bauer, Ph.D. CBER/OTAT/DCGT/CTTB	3.2.S.2.3 Consult review for (b) (4)
Elena Gubina, Ph.D. CBER/OTAT/DCGT/GTB	3.2.S.2.3 Consult review for (b) (4)
Sukhanya Jayachandra, Ph.D. CBER/OTAT/DCGT/CTB	3.2.S.2.3 Consult review for (b) (4)
Laura Ricles, Ph.D CBER/OTAT/DCGT/CTB	3.2.P.7 Consult Review for (b) (4)
Guo-Chiuan Hung, Ph.D. OTAT/DCGT/GTIB	3.2.S.2.3 Consult review for (b) (4)

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Rong Wang, CDER/OPQ/OBP/DBRRIII	DMF (b) (4) (b) (4)	Yes

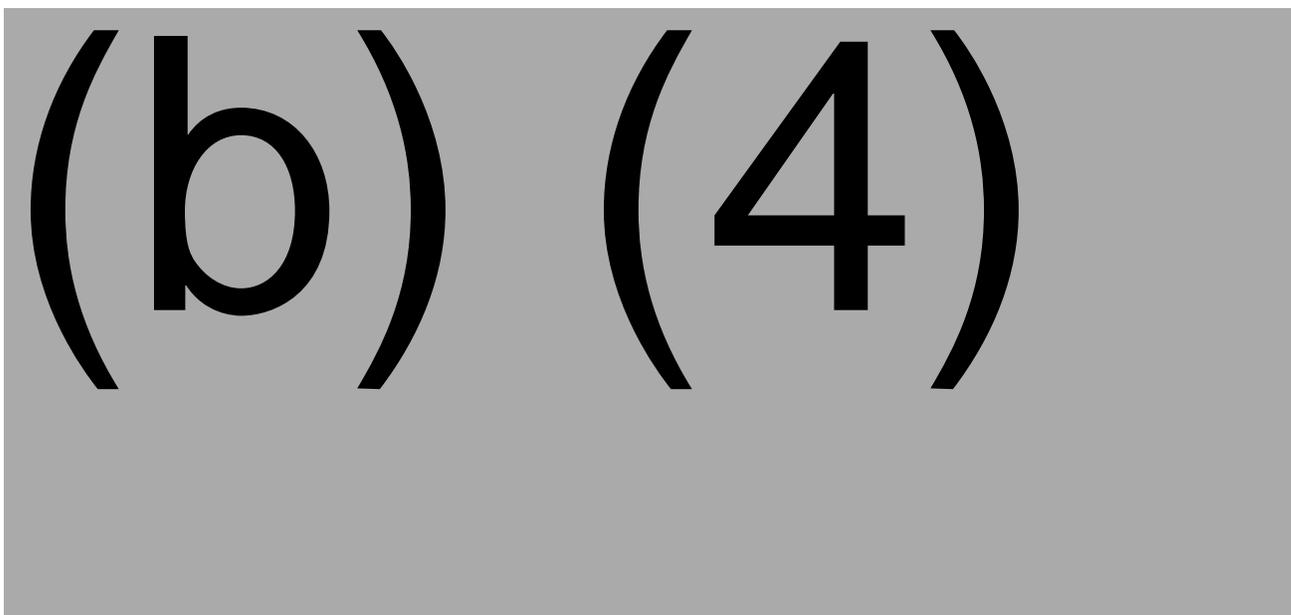
8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/Status
10/13/2019	125714/0	Preclinical section
11/1/2019	125714/1	Clinical section
12/18/2019	125714/3	Quality section and updated Clinical Section Completed submission of rolling BLA
1/14/2020	125714/4	Response to CMC IR #2 dated 1/5/2020
1/16/2020	125714/5	(b) (4) facility regarding ongoing facility improvements
1/27/2020	125714/6	Response to CMC IR #3 dated 1/13/2020 and 1/17/2020
2/7/2020	125714/8	(b) (4) facility regarding ongoing facility improvements
2/20/2020	125714/11	Response to CMC IR#9 dated 2/10/2020 (partial)
2/26/2020	125714/13	JuMP (b) (4) contamination report
2/21/2020	125714/15	Application Orientation Meeting Materials
3/9/2020	125714/16	Response to CMC DMPQ IR#11 dated 2/18/2020

3/10/2020	125714/17	Response to CMC IR#12 dated 02/27/2020
3/13/2020	125714/18	Response to CMC IR#9 dated 2/10/2020
3/26/2020	125714/22	Response to CMC IR#20 dated 3/16/2020
3/30/2020	125714/23	Response to CMC IR#21 dated 3/19/2020 (partial)
4/1/2020	125714/24	Response to CMC IR #23 dated 3/24/2020
4/3/2020	125714/25	Response to CMC IR#21 dated 3/19/2020, CMC IR#22 dated 3/23/2020 (partial)
4/7/2020	125714/26	Response to CMC DMPQ IR#17 dated 3/6/2020, CMC IR#22 dated 3/23/2020
3/17/2020	125714/29	Response to CMC OCBQ IR#13 dated 2/28/2020
4/9/2020	125714/28	Response to CMC IR#27
4/14/2020	125714/30	Response to CMC IR#28 dated 4/6/2020, CMC IR#31 dated 4/6/2020
4/15/2020	125714/31	Response to CMC IR#22 dated 3/23/2020
4/16/2020	125714/32	Sponsor Midcycle Minutes
4/21/2020	125714/33	Response to CMC DBSQC IR#33 dated 4/14/2020
4/24/2020	125714/51	Response to CMC IR#34 dated 4/14/2020, CMC IR#36 dated 4/16/2020
4/27/2020	125714/34	Response to CMC DMPQ IR#30 4/27/2020
4/29/2020	125714/35	Response to CMC IR#38 dated 4/20/2020
5/5/2020	125714/37	Response to CMC IR#40 dated 4/23/2020, CMC IR#44 dated 4/29/2020
5/6/2020	125714/38	Response to CMC IR#42 dated 5/6/2020
5/18/2020	125714/42	Response to CMC IR#48 dated 5/14/2020
5/26/2020	125714/44	Response to CMC IR#47 dated 5/11/2020
6/16/2020	125714/49	Response to CMC IR#52 dated 6/4/2020 (partial), CMC DMPQ IR#55 dated 6/11/2020
6/18/2020	125714/50	CMC IR#56 dated 6/12/2020
6/19/2020	125714/52	JuMP PLI documents
6/26/2020	125714/53	Response to CMC IR#52 dated 6/4/2020
6/29/2020	125714/54	(b) (4) PLI documents
7/17/2020	125714/56	Response to CMC DMPQ IR#59 dated 7/17/2020
7/21/2020	125714/57	Response to CMC IR#61 dated 7/9/2020, CMC IR#30 dated 4/8/2020, CMC IR#52 dated 6/4/2020
7/21/2020	125714/58	Response to CMC IR#60 dated 7/7/2020
7/28/2020	125714/59	Response to CMC IR#62 dated 7/15/2020
8/4/2020	125714/60	Response to CMC IR#63 dated 7/23/2020, CMC IR#65 dated 7/29/2020
8/19/2020	125714/61	Response to CMC IR#66 dated 8/7/2020
8/21/2020	125714/62	CMC IR#67 dated 8/13/2020
8/28/2020	125714/63	CMC IR#70 dated 8/25/2020; agree to PMC language and report date
9/10/2020	125714/65	Module 3 updates following the Late Cycle Meeting
9/16/2020	125714/69	Juno's minutes from the Late Cycle meeting held on 09/02/2020
9/21/2020	125714/71	CMC IR#73 dated 9/10/2020

10/5/2020	125714/74	JuMP PLI record request documents
10/6/2020	125714/75	Labeling IR#76 dated 09/25/2020
10/6/2020	125714/76	CMC IR#77 dated 09/28/2020
10/7/2020	125714/77	(b) (4) PLI record request documents
10/14/2020	125714/78	Labeling IR#79 dated 10/07/2020
10/27/2020	125714/80	CMC IR#81 dated 10/16/2020
10/28/2020	125714/81	Labeling IRs #82 dated 10/19/2020, #83 dated 10/19/2020, and #84 dated 10/19/2020
11/5/2020	125714/82	Labeling IR #85 dated 10/29/2020
11/6/2020	125714/83	Responses to 483 observations from the JuMP PLI
11/6/2020	125714/84	Clinical AE report
11/12/2020	125714/86	Labeling IR #89 dated 11/05/2020
11/13/2020	125714/87	Labeling IR #91 dated 11/10/2020
11/12/2020	125714/90	Applicant name change to Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
12/7/2020	125714/91	follow up AE report
12/9/2020	125714/92	Response to additional information requested regarding the JuMP PLI
12/18/2020	125714/93	Responses to 483 observations from the (b) (4) PLI
12/18/2020	125714/94	Response to additional information requested regarding the JuMP PLI
12/23/2020	125714/95	Response to additional information requested regarding the (b) (4) PLI
12/28/2020	125714/96	Response to additional information requested regarding the AE report in amendment 84

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



10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The CMC review team concludes that the manufacturing process, along with the test methods and control measures, for lisocabtagene maraleucel is capable of yielding autologous products with consistent quality attributes. The prelicense inspections (PLI) were postponed due to COVID-19-related travel restrictions and the action due date of November 16, 2020 was missed. Since that time, the PLIs have been completed and inspection-related issues are resolved. The CMC review team recommends approval.

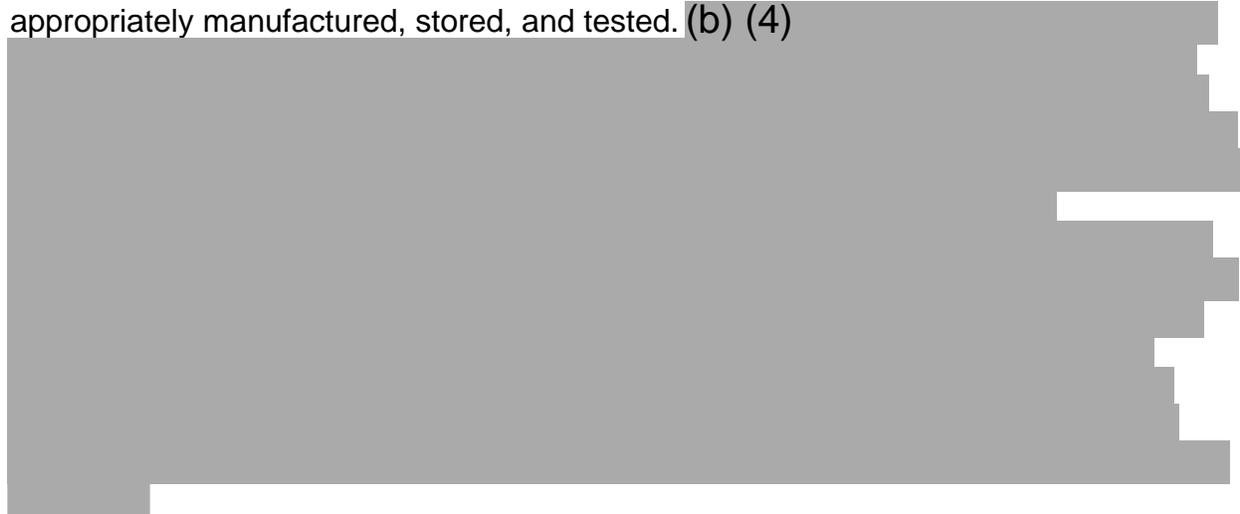
Lisocabtagene maraleucel (referred to throughout this document as JCAR017) is composed of autologous CD8 and CD4 T cells that are genetically modified with a lentivirus vector (b) (4) encoding a chimeric antigen receptor (CAR) that specifically recognizes the CD19 protein present on (b) (4) as well as (b) (4). Lisocabtagene maraleucel is manufactured from autologous leukapheresis material that is selected sequentially for the CD8 and CD4 positive T cells, which are then activated, transduced, expanded, and formulated separately. The CD8 and CD4 drug products (DPs) are packaged together to constitute a single dose of lisocabtagene maraleucel. Neither the CD4 or CD8 DP can be released alone, therefore the separately manufactured DPs are referred to as components of the complete CAR T cell therapy. Lisocabtagene maraleucel is formulated at (b) (4) into an infusible cryopreservation solution (b) (4) Multiple Electrolytes Injection, Type I, (b) (4) human serum albumin (HSA), 75% CryoStor® CS10), filled into four 5 mL cryopreservation vials per DP, and stored at $\leq -130^{\circ}\text{C}$. Lot release testing is conducted on each CD8 and CD4 DP to determine product quality and the DPs are infused sequentially (first CD8 DP then CD4 DP) at a 1:1 ratio of CAR-positive T cells within the acceptable dose range of $50 \times 10^6 - 110 \times 10^6$ CAR positive T cells. The DPs are provided sterile and no preservatives are included in the cryopreservation medium (DMSO). Lisocabtagene maraleucel is shipped frozen in a dry liquid nitrogen shipper, with the product vials (1 to 4 vials per DP) stored inside of a carton secured in a metal rack. Lisocabtagene maraleucel is stored in vapor phase liquid nitrogen ($\leq -130^{\circ}\text{C}$) until required, when it is thawed and infused within 2 hours.

Manufacturing and quality.

There are (b) (4) drug substances (DS) required for lisocabtagene maraleucel manufacturing: the (b) (4) vector, (b) (4). The CAR encoded in the (b) (4) vector is composed of the FMC63 murine anti-human CD19-specific antibody single chain variable fragment (scFv) (b) (4) human 4-1BB and the CD3 ζ intracellular domain (b) (4). The vector also encodes the truncated Epidermal Growth Factor Receptor (EGFRt). When transduced into the autologous T cells, the CAR directs the intended mode of action for lisocabtagene maraleucel.

The (b) (4) vector is a nonreplicating, self-inactivated lentivirus, based on (b) (4). The (b) (4) is manufactured at a contract manufacturing facility ((b) (4) Master and working cell banks (WCB) used for (b) (4) production have been

appropriately manufactured, stored, and tested. (b) (4)



The CAR T cell DPs are manufactured using leukapheresis material collected from patients at qualified apheresis centers. Due to the autologous nature of the product the Chain of Identity/Chain of Custody (COI/COC) is established at the collection site and are maintained through the manufacturing process and administration by conducting label checks at specified times. The leukapheresis material is shipped to the JuMP manufacturing facility (Bothell, WA) where it is inspected, and the manufacturing process is initiated. The leukapheresis material is washed and separated (b) (4)

The two selected components are independently cryopreserved. (b) (4)

Each component is activated with anti-CD3 (b) (4), transduced with the (b) (4) vector, and expanded in culture until (b) (4)

The cells are washed and (b) (4)

Multiple Electrolytes Injection, Type I, (b) (4) human serum albumin (HSA), 75% CryoStor[®] CS10). The formulated cells are (b) (4) aliquoted into four 5 mL (b) (4) cryovials. Filled final product vials are examined for appearance, then cryopreserved using a controlled rate freezer and stored at $\leq -130^{\circ}\text{C}$ in vapor phase liquid nitrogen until lot release testing is complete. The lot release testing results are used to determine the volume of each DP component required to meet the target dose. The number of 5 mL vials (1-4 vials each) that are required for administration of each DP are packaged into the secondary packaging and the released DPs are then shipped in a liquid nitrogen dewar to treatment sites for administration to the patient. During the BLA review, the target cell concentration of formulated DP was adjusted in order to reduce the amount of excess DP released to clinical sites.

The control strategy begins with material qualification. Raw materials and reagents are accepted based on specified quality attributes, including identity, concentration, and purity. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants. All samples for lot release testing are collected at the appropriate stages in manufacture: (b) (4) test samples are taken from (b) (4); sterility is assessed in the final formulated DP prior to cryopreservation and all other tests are performed (b) (4) DP in QC vials. Lot release test methods are suitably validated, or verified for compendial assays, and product specifications are adequate to ensure product quality and consistency with DP used in the clinical study.

Stability

DP stability at ≤-130°C in vapor phase liquid nitrogen for long term storage is determined to be 13 months. Stability was assessed using healthy donor and patient-derived lots using the commercial manufacturing process. The studies assessed a range of cellular concentrations, which supports stability using the adjusted formulation calculation. The DP is stable for 2 h after thaw allowing for dose preparation into syringes 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 lisocabtagene maraleucel. 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, along with post-marketing commitments (PMC) from Juno Therapeutics, Inc., 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. The review team recommends regular approval of this BLA.

Manufacturing facilities:

The following facilities are used for manufacturing and testing of the (b) (4) vector drug substance (DS), and the lisocabtagene maraleucel DS and drug product (DP):

- (b) (4) [Redacted]
- Juno Therapeutics Inc, 400 Dexter Ave N, Suite 1200 Seattle, WA 98109 USA

CBER Lot release:

lisocabtagene maraleucel has been deemed exempt from CBER lot release testing and protocol review.

Post-Marketing Commitments

1. *Juno Therapeutics, Inc., commits to prospectively validate the (b) (4) [redacted] per protocol (b) (4) [redacted] and will provide the validation report.*

Final Study Report Submission: September 30, 2021

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Kimberly LW Schultz, Ph.D. Review Committee Chair Biologist CBER/OTAT/DCGT/GTB	Concur	
Nirjal Bhattarai, Ph.D. Senior Staff Fellow CBER/OTAT/DCGT/GTIB	Concur	
Tiffany Lucas, Ph.D. Biologist CBER/OTAT/DCGT/GTB	Concur	
Denise Gavin, Ph.D. Branch Chief, Gene Therapy Branch CBER/OTAT/DCGT/GTB	Concur	
Steven Oh, Ph.D. Deputy Director, Division of Cellular and Gene Therapies CBER/OTAT/DCGT	Concur	
Raj Puri, M.D. Ph.D. Director, Division of Cellular and Gene Therapies CBER/OTAT/DCGT	Concur	

Review of CTD

Table of Contents

3.2.S DRUG SUBSTANCE: (b) (4) (Lentiviral vector) 13

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

 3.2.S.2 Manufacture 14

 3.2.S.2.1 Manufacturer(s) 14

 3.2.S.2.2 Description of Manufacturing Process 16

 3.2.S.2.3 Control of Materials 20

 3.2.S.2.4 Controls of Critical Steps and Intermediates 29

 3.2.S.2.5 Process Validation and/or Evaluation 33

 3.2.S.2.6 Manufacturing Process Development 42

 3.2.S.3 Characterization 45

 3.2.S.3.1 Elucidation of Structure and Other Characteristics 45

 3.2.S.3.2 Impurities 45

 3.2.S.4 Control of Drug Substance 46

 3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s) 46

 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures 51

 3.2.S.4.4 Batch Analyses 94

 3.2.S.5 Reference Standards or Materials 95

 3.2.S.6 Container Closure System 96

 3.2.S.7 Stability 97

 3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data 97

 3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment 102

3.2.S DRUG SUBSTANCE: (b) (4) 102

 3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties 102

 3.2.S.2 Manufacture 103

 3.2.S.2.1 Manufacturer(s) 103

 3.2.S.2.2 Description of Manufacturing Process 103

 3.2.S.2.3 Control of Materials 107

 3.2.S.2.4 Controls of Critical Steps and Intermediates 116

 3.2.S.2.5 Process Validation and/or Evaluation 121

 3.2.S.2.6 Manufacturing Process Development 121

 3.2.S.3 Characterization 121

 3.2.S.3.1 Elucidation of Structure and Other Characteristics 121

 3.2.S.3.2 Impurities 124

 3.2.S.4 Control of (b) (4) Drug Substance (b) (4) DS) 126

 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures 126

 3.2.S.4.4 Batch Analyses 126

 3.2.S.5 Reference Standards or Materials 126

 3.2.S.6 Container Closure System 126

 3.2.S.7 Stability 126

3.2.S DRUG SUBSTANCE: (b) (4) 126

 3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties 126

 3.2.S.2 Manufacture 127

3.2.S.2.1 Manufacturer(s) 127

3.2.S.2.2 Description of Manufacturing Process 127

3.2.S.2.3 Control of Materials 127

3.2.S.2.4 Controls of Critical Steps and Intermediates 127

3.2.S.2.5 Process Validation and/or Evaluation 128

3.2.S.2.6 Manufacturing Process Development 128

3.2.S.3 Characterization 128

3.2.S.3.1 Elucidation of Structure and Other Characteristics 128

3.2.S.3.2 Impurities 130

3.2.S.4 Control of (b) (4) Drug Substance (b) (4) DS) 131

3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s) 131

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures
..... 131

3.2.S.4.4 Batch Analyses 131

3.2.S.5 Reference Standards or Materials 131

3.2.S.6 Container Closure System 131

3.2.S.7 Stability 132

3.2.P DRUG PRODUCT: CD8 132

3.2.P.1 Description and Composition of the Drug Product 132

3.2.P.2 Pharmaceutical Development 132

3.2.P.2.1 Components of the Drug Product 132

3.2.P.2.2 Drug Product 133

3.2.P.2.3 Manufacturing Process Development 140

3.2.P.2.4 Container Closure 152

3.2.P.2.5 Microbiological Attributes 153

3.2.P.2.6 Compatibility 153

3.2.P.3 Manufacture 154

3.2.P.3.1 Manufacturer(s) 154

3.2.P.3.2 Batch Formula 154

3.2.P.3.3 Description of Manufacturing Process 155

3.2.P.3.4 Controls of Critical Steps and Intermediates 156

3.2.P.3.5 Process Validation and/or Evaluation 157

3.2.P.4 Control of Excipients 172

3.2.P.4.1 Specifications 172

3.2.P.4.2, 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures
..... 173

3.2.P.4.4 Justification of Specifications 174

3.2.P.4.5 Excipients of Human or Animal Origin 174

3.2.P.4.6 Novel Excipient 174

3.2.P.5 Control of Drug Product 174

3.2.P.5.1 Specification(s) 174

3.2.P.5.6 Justification of Specification(s) 176

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical
Procedures 186

3.2.P.5.4 Batch Analyses 205

3.2.P.5.5 Characterization of Impurities 207

3.2.P.6 Reference Standards or Materials 207

3.2.P.7 Container Closure System..... 208

3.2.P.8 Stability 211

 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data 211

 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment 220

3.2.P DRUG PRODUCT: CD4 220

 3.2.P.1 Description and Composition of the Drug Product..... 220

 3.2.P.2 Pharmaceutical Development..... 221

 3.2.P.2.1 Components of the Drug Product 221

 3.2.P.2.2 Drug Product 221

 3.2.P.2.3 Manufacturing Process Development..... 222

 3.2.P.2.4 Container Closure System 222

 3.2.P.2.5 Microbiological Attributes 222

 3.2.P.2.6 Compatibility 222

 3.2.P.3 Manufacture 222

 3.2.P.3.1 Manufacturer(s) 222

 3.2.P.3.2 Batch Formula 222

 3.2.P.3.3 Description of Manufacturing Process..... 223

 3.2.P.3.4 Controls of Critical Steps and Intermediates 223

 3.2.P.3.5 Process Validation and/or Evaluation..... 223

 3.2.P.4 Control of Excipients 223

 3.2.P.5.1 Specification(s)..... 223

 3.2.P.5.6 Justification of Specification(s) 223

 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical
Procedures 223

 3.2.P.5.4 Batch Analyses..... 224

 3.2.P.5.5 Characterization of Impurities..... 224

 Characterization of Impurities is reviewed in section 3.2.S.3.2 Impurities of this BLA
review. 224

 3.2.P.6 Reference Standards or Materials 224

 3.2.P.7 Container Closure System..... 224

 3.2.P.8 Stability 224

 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data 224

 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment 224

3.2.A APPENDICES 224

 3.2.A.1 Facilities and Equipment 224

 3.2.A.2 Adventitious Agents Safety Evaluation 227

 3.2.A.3 Novel Excipients 228

3.2.R Regional Information (USA) 228

Other eCTD Modules 229

 A. Environmental Assessment or Claim of Categorical Exclusion 229

 B. Labeling Review 230

 Analytical Procedures and Validation of Analytical Procedures for Assessment of
Clinical and Animal Study Endpoints 235

Module 3

3.2.S DRUG SUBSTANCE: (b) (4) (Lentiviral vector)

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

Reviewed by KLWS

Nomenclature: The company code for the lentivirus vector used in the manufacture of JCAR017 is (b) (4). A USAN/INN name will not be assigned for the vector.

Structure and General Properties: (b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Reviewed by TML. Tables are prepared by TML from information provided in 125714.

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

Reviewer comment: The original BLA submission initially listed several (b) (4) release assays that would be performed at (b) (4) US (b) (4) sites. Through the review process it was determined that there was insufficient information to support assay use at the (b) (4) testing site, as the product-specific qualification (PSQ) was only performed at the US site and Juno did not provide data to support assay use at (b) (4) testing site. Therefore, Juno removed (b) (4) site for testing (b) (4) . (Amendment 31, 04/15/2020). (b) (4) will only be performed at (b) (4) (Amendment 44, received on 05/28/2020) due to insufficient assay validation at (b) (4)

3.2.S.2.2 Description of Manufacturing Process

Reviewed by KLWS

Overview: The lentiviral vector (b) (4) is manufactured by (b) (4). The vector is (b) (4) to cryopreservation. The (b) (4) lentiviral vector manufacturing process does not allow for (b) (4) of any unit operations for (b) (4).

- (b) (4)

(b) (4)

(b) (4)

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

Overall Reviewer’s Assessment of Section 3.2.S.2.4:

TML: The control of critical steps and intermediates is adequately supported. CPP, KPPs, operating ranges, and in-process controls are defined and described sufficiently. Storage conditions are appropriate. Courier and shipping container and logger specifics are adequate in combination with material reviewed in section 3.2.S.2.5 Process Validation and/or Evaluation.

KLWS: The (b) (4) may be (b) (4) manufacturing. The (b) (4) shelf-life can be (b) (4) following successful completion of the proposed stability study.

3.2.S.2.5 Process Validation and/or Evaluation

Reviewed by KLWS

The (b) (4) process validation is composed of (b) (4) studies are reviewed in section 3.2.S.2.6 Manufacturing Process Development.

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

Overall Reviewer’s Assessment of Section 3.2.S.2.5:

The original submission did not provide adequate information for review. The (b) (4) (b) (4) validation reports were provided upon request in Amendment 6 (received 1/27/2020) and the (b) (4) Plan was provided in Amendment 57 (received on 7/21/2020).

The process validation demonstrates adequate control of (b) (4) manufacturing in order to support consistent vector manufacturing necessary for use in the CAR T cell manufacturing process. The PPQ results indicate that the proposed commercial manufacturing process, which was refined prior to the BLA submission, produce a vector with consistent quality attributes. The provided information indicates that the (b) (4) shipping configuration and controls are adequate to maintain the target temperature.

3.2.S.2.6 Manufacturing Process Development

Reviewed by KLWS

Process development History:

(b) (4)

(b) (4)

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

Overall Reviewer's Assessment of Section 3.2.S.2.6:

Adequate information was provided on the (b) (4) development and process characterization to support the commercial manufacturing process and identified process parameters ranges necessary to maintain (b) (4) quality.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

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

(b) (4)

Overall Reviewer’s Assessment of Sections 3.2.S.4.1 and 3.2.S.4.5:
 The final specifications and justification for (b) (4) are adequate. CMC analyzed data by including only lots manufactured with the current manufacturing method (i.e., (b) (4) lots were excluded from data analysis used for release criteria) and asked Juno to update release criteria to reflect data obtained by lots reflective of the manufacturing process. Release criteria were adequately updated in Amendment 44 (received on 05/26/2020), the (b) (4) in Amendment 49 (received on 06/16/2020), and (b) (4) in Amendment 61 (received on 08/19/2020).

Release criteria for (b) (4) were updated in BLA Module 3 with the submission of amendment 65 (received on 09/10/2020).

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures
 Reviewed by TML. Tables are designed by TML from data provided in 125714.

Juno received a Major Amendment Acknowledgement letter from the FDA on 05/05/2020 due to information submitted for review in Amendment 31 (received on 04/15/2020). Amendment 31 included analytical procedures and validation reports for all (b) (4) tests performed at (b) (4), with the exception of 2 validation reports provided in Amendment 51 (received on 04/29/2020). The original BLA submission contained, in most cases, summaries of assays and platform validations performed at contract testing organizations, which was inadequate to understand and assess control of the (b) (4) analytical procedures and respective validations.

The following information requests were required to obtain adequate assay and validation information (formatted as amendment number, date received: description):

- (b) (4)

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

(b) (4)



Product contact components used in manufacturing of JCAR017: A list of product contact components used in manufacturing of JCAR017 is listed in Table 57:

Table 57 Raw materials that come in contact with product during manufacturing



Reviewer comment: A risk assessment was conducted for all product contacting materials. Product contacting materials with the highest risk to contribute impurities to the DP were selected for extractable and leachable testing and is discussed in Section 3.2.P.3.5 Process Validation and/or Evaluation of this BLA review. No significant concerns were identified. Acceptable.

Control of Starting (i.e., Source) Material(s)

Leukapheresis material is the patient-specific starting cellular material for JCAR017 DS manufacturing. The leukapheresis material is collected at centers that have been qualified by Juno. The collections are performed according to written procedures by staff that have the education, training, and experience required to meet state and local requirements for this activity. Requirements related to the collection of the leukapheresis material, including equipment, equipment settings, materials, run targets, subject identity verification, labeling, and packaging are provided in writing to each collection center by Juno. The patient leukapheresis material is collected using an

(b) (4)



(b) (4)



(b) (4)



Leukapheresis stability and shipping validation studies are discussed in Section 3.2.P.3.5 Process Validation and/or Evaluation of this BLA review.

Chain of identity (COI): COI is ensured by a program that implements central policy oversight, local SOPs and risk management, and a combination of validated systems and interfaces. At every step in the treatment cycle, from leukapheresis collection to DP administration, COI is checked and verified independently by (b) (4) individuals prior to execution of subsequent processing using human-readable label information and barcode scanner. When a patient is scheduled for leukapheresis collection, a patient specific JOIN, a unique alphanumeric sequence, is assigned. The JOIN is used as the basis for COI controls throughout production. Patient identifying information (PII) comprising of the patient's first name, last name, and date of birth (DOB), along with the JOIN are used to verify patient identity during patient collection and product infusion operations. Prior to initiating collection of the leukapheresis material, collection center staff verify the patient's identity to the PII using a legal form of identification. Once identity is confirmed, a label that contains the JOIN and the PII is affixed to the leukapheresis collection bag. The JOIN, manufacturing lot number, and a scannable bar code is used to track COI throughout production at the manufacturing facility. See 3.2.A.1 Facilities and Equipment of this BLA review for additional information on the control of COI and COC.

Incoming leukapheresis material is (b) (4)
External packaging identifies the contents as subject cells, and the shipment is staged in a segregated, secure location. Upon receipt at the manufacturing site, the leukapheresis material is inspected to ensure COI and product integrity. After inspection, the product is transferred into the manufacturing suite to initiate manufacturing. Juno leukapheresis material stability studies demonstrated that the leukapheresis material can be (b) (4).

Leukapheresis stability studies are discussed in Section 3.2.P.3.5 Process Validation and/or Evaluation of this BLA review.

Reviewer comment:

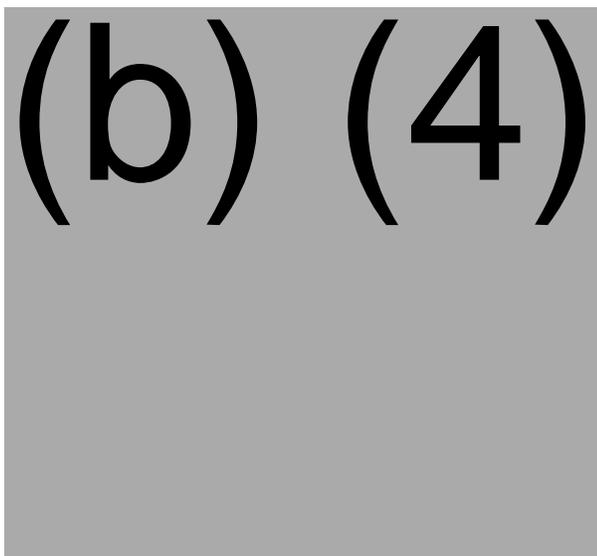
1. *The starting leukapheresis material is collected using a standard process directly into (b) (4). The overall risk for leukapheresis material to be contaminated is minimal. Acceptable.*

2. *In Amendment 37 (received on 5/5/2020), Juno provided additional information on the leukapheresis bag and label. The patient leukapheresis material is collected using an (b) (4)*

This is acceptable.

3. *Leukapheresis bag labels will either be printed by Juno and shipped to the leukapheresis collection site prior to the collection date or printed at the collection site (b) (4) on label stock provided by Juno (label example: Figure 12).*

Figure 12 Example Commercial Leukapheresis Label



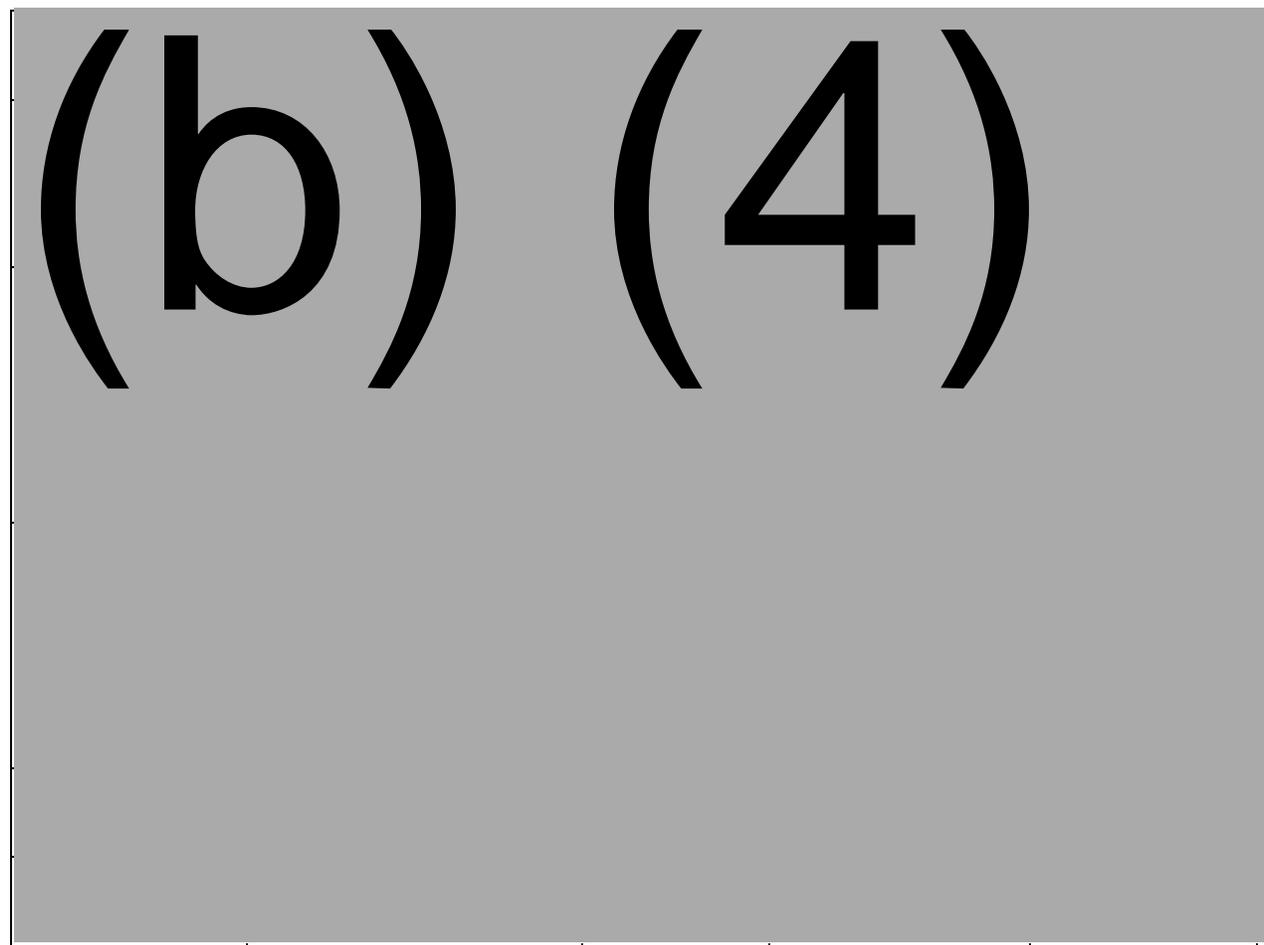
Overall Reviewer’s Assessment of Section 3.2.S.2.3: The information provided in the original BLA was incomplete to assess if adequate procedures are in place to control raw materials and leukapheresis material. Additional information was provided in Amendments 37, 49, and 59 as noted in the review. The additional information obtained in response to IRs are acceptable and provide assurance that raw materials and leukapheresis material are under control.

3.2.S.2.4 Controls of Critical Steps and Intermediates

Reviewed by NB

Juno has established a defined set of controls based on their current understanding of the DP manufacturing process. The controls are designated as process parameters, in-process controls, or processing times. Process parameters are classified as critical process parameters (CPPs) or non-critical process parameters (nCPPs). In-process controls (IPCs) are associated with either acceptance criteria or action limits. Processing times are associated with limits. CPPs and IPCs are listed for each unit operation. This determination of criticality was based on the risk analysis and experimental work (3.2.P.2.3 Manufacturing Process Development). Acceptable ranges are provided for CPPs (Table 58) and IPCs (Table 59) to ensure that the process consistently delivers JCAR017 DPs that meet product quality requirements.

(b) (4)



(b) (4)

Reviewer comment: In the original submission, Juno provided acceptable ranges for CPPs and acceptance criteria and action limits for IPCs; however, it was unclear how these criteria were established. In Amendment 17 (received on 03/10/2020), Juno provided justification. For CPPs, the acceptable ranges were established based on the characterization data and range at which product quality met clinical specifications. If acceptable product quality was not met across the characterized range, the acceptable range was adjusted to a range within the characterized range to a point where acceptable product quality were predicted to be met based on modeled data. Similarly, acceptance criteria for IPCs were established based on product characterization data and clinical data. Acceptable.

Microbial Contamination Controls: Microbial contamination is controlled by using aseptic techniques, using raw materials that have been qualified and manufacturing the drug substance in separate and secure areas that have protective procedures designed to prevent microbial contamination. For information on environmental monitoring during manufacturing, please refer to the review by Rabia Ballica, OCBQ/DMPQ for details. Briefly, information submitted indicates low risk of microbial contamination during processing.

(b) (4)

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

Overall Reviewer’s Assessment of Section 3.2.S.2.4: In the original submission, Juno did not provide sufficient information on how CPPs and IPCs were established and information provided on stability and container closure of stored intermediates were inadequate. In Amendments 17, 37, and 63 described above, Juno provided responses to these deficiencies. Consequently, the CMAT shelf-life is set at (b) (4) months. Acceptable.

3.2.S.2.5 Process Validation and/or Evaluation

The process validation for the DS is included in the DP Process Validation Reviewed in 3.2.P.3.5 Process Validation and/or Evaluation

3.2.S.2.6 Manufacturing Process Development

Manufacturing Process Characterization is reviewed in 3.2.P.2.3 Manufacturing Process Development

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

Reviewed by NB

JCAR017 CD8 and CD4 DPs are manufactured and formulated separately to enable controlled dosing of both DPs. JCAR017 DPs expresses the same CD19-targeted CAR (Table 1) comprised of five distinct domains with four key properties: Extracellular FMC63 single chain variable fragment (scFv) for (b) (4), IgG4 hinge provides (b) (4)

(b) (4) CD28 transmembrane domain (b) (4) CD3ζ activation and 4-1BB costimulatory domains provide intracellular signals for T cell function. In addition, DP expresses a nonfunctional extracellular protein, EGFRt that has been used as a (b) (4)

1. JCAR017 CAR Structural Assessment

(b) (4)

(b) (4)

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

CR. Juno states that these assessments are exploratory in nature and cannot be conclusive at this point. Juno intends to collect more data to assess any correlation between DP quality attributes and clinical safety and efficacy. [Acceptable](#).

3.2.S.3.2 Impurities

Reviewed by KLWS

Process-related impurities:

Process related impurities are mainly removed by (b) (4). Impurity measurements were included in the PPQ studies found in section 3.2.P.3.5 Process Validation and/or Evaluation (Table 84), which demonstrated adequate removal of a variety of process-related impurities including (b) (4).

Process-related impurity analysis was supported by data from (b) (4) DP lots manufactured using the proposed commercial manufacturing process.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

Reviewer comment: Juno states that post-hoc correlative analysis was exploratory and did not find any definitive correlations between the CD4 DP quality attributes and clinical safety, efficacy, or PK. While this is true as this assessment was based on a small data size, several potential relationships were identified, and these potential relationships remain of interest. Juno states that they will continue to characterize these quality attributes to better understand overall strength and clinical significance of these potential relationships. This justification is acceptable. In addition, some of the identified attributes such as viability is assessed and controlled as part of DP lot release specifications.

3.2.S.3.2 Impurities

Reviewed by KLWS

Process-related Impurities: The process-related impurities in the CD4 DP are similar to those in the CD8 DP reviewed in section 3.2.S.3.2 Impurities.

(b) (4)

Reviewer comment: The additional CD4 DP-specific information is appropriate to supplement the referenced CD8 DP section.

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT: CD8

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

Reviewed by KLWS

JCAR017 is formulated as a single-dose cell suspension for infusion composed of autologous CD8 and CD4 DPs expressing the CD19-specific CAR. The CD8 DP is individually manufactured, formulated, and cryopreserved into cryogenic vials composed of (b) (4) (4 vials per drug product component). Each vial contains $\geq 1.5 \times 10^6$ CAR+ viable T cells/mL.

Reviewer comment: The minimum viable T cell concentration was updated in Amendment 80 (received on 10/27/2020) in association with the communication by the FDA clinical review team for the approved dose.

3.2.P.2 Pharmaceutical Development

Reviewed by KLWS

3.2.P.2.1 Components of the Drug Product

JCAR017 is composed of equal amounts of CD4 and CD8 CAR-T cells. The CD8 DP is composed of the CAR-expressing (b) (4).

Table 63 JCAR017 CD8 DP composition

Constituent	Quality Standard/Grade	Function	Target Concentration
CAR+ viable CD8+ T cells	In-house	Active	$\geq 1.5 \times 10^6$ CAR+ viable T cells/mL ^a
Cryostor® CS10 (containing (b) (4) DMSO)	In-house	(b) (4)	75% [v/v] ^b
Multiple Electrolytes Injection, Type I (b) (4)	(b) (4)	(b) (4)	(b) (4) [v/v]
Albumin (Human) Solution (25% Albumin) (b) (4)	(b) (4)	(b) (4)	(b) (4) [v/v] ^c

a Extractable volume: 4.6 mL per vial

b Final DMSO concentration in drug product is 7.5%.

c Final Albumin concentration in drug product is (b) (4).

3.2.P.2.1.1 Drug Substance

The (b) (4) is mostly composed of (b) (4) vector. The percentage of (b) (4) varies within an allowable range for each patient lot. (b) (4) are the most common impurity. Compatibility of the JCAR017 with the excipients has been established during clinical development and in studies described in 3.2.P.2.2.1 Formulation Development of this BLA review.

3.2.P.2.1.2 Excipients

All excipients listed in Table 63 above except CryoStor (DMSO) are licensed drugs for injection. CryoStor has been used in FDA-licensed HPC, cord blood products to levels of up to 10%; the intended formulation results in 7.5% DMSO. CryoStor is a synthetic material that is part of the final formulation of previously licensed CAR-T cells and is reviewed under CBER MF (b) (4). The excipients provide the necessary (b) (4) of the formulation (b) (4).

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The commercial formulation process was established during the IND with manufacturing process (b) (4) when the 5 mL (b) (4) Vials were chosen as the final container. Manufacturing process (b) (4) formulations contained neat Cryostor (b) (4) DMSO) in a cryopreservation bag. The formulation used for manufacturing process (b) (4) is the proposed commercial formulation containing Cryostor CS10 (10% DMSO) (b) (4) Multiple Electrolytes Injection, Type I and albumin (human) to achieve 7.5% DMSO in a cryopreservation vial. The change in formulation from manufacturing (b) (4) per DP, requiring an (b) (4). Juno indicates that this change (b) (4) correlated with (b) (4). Juno evaluated the effect of (b) (4), DMSO concentration, and HSA concentration on product stability at (b) (4). The tested CQAs were not affected by the varied excipient concentrations. (b) (4) was affected when the (b) (4).

Reviewer comment: The varied excipient concentrations had no effect on CQAs in any of the test conditions. Additional studies were conducted as part of the process characterization studies in 3.2.P.2.3 Manufacturing Process Development that complement these studies to inform recommendations for the allowable final cell concentration. Acceptable.

Overfill:

The formulation process results in (b) (4) of overfill included in the DP:

1. *Extractable volume:* Each (b) (4) vial is filled with 5 mL of formulated JCAR017, with an extractable volume of 4.6 mL. Extraction studies (provided in Amendment

37, received on 05/05/2020) indicate that (b) (4) is consistently extracted from the vials with (b) (4) held over in the syringe (Table 64).

Table 64 CellSeal extractable volume

Nominal Syringe Size	Target Extractable Volume (mL)	Volume Delivered (mL)	Residual Syringe Volume (mL)
		(b) (4)	
3 mL syringe	(b) (4)	(b) (4)	
5 mL syringe	4.6	(b) (4)	

Reviewer comment: The studies indicate that the remaining volume left in the syringe is minimal, (b) (4) of the dose is retained, and should not impact dosing.

2. *Excess product after dose determination:* The JCAR017 formulation procedure is based on (b) (4). JCAR017 is provided in up to four 5 mL vials of each DP, with the clinical site preparing the exact dose according to the Release For Infusion certificate provided with each lot that indicates the volume of each DP to be administered. Consequently, excess DP is provided to the clinical site and is disposed of after dose preparation.

Reviewer comment: Formulation based on (b) (4) is justified by highly variable post-thaw recoveries. If the formulated dose is determined prior to thaw, then the post thaw recovery affects the amount of product available in the final dose, resulting in lower than intended doses provided to patients. By determining the dose volume post thaw, a more consistent dose should be delivered, however, the excess product released raises the possibility of medical errors. The 2015 FDA guidance entitled Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products recommends that the excess volume generally should not be sufficient to provide a second dose.

The formulation process was discussed during the IND stage; however, it was not clear at that time that the provided excess DP was often more than (b) (4) the administered dose; (b) (4) for the CD8 DP and (b) (4) for the CD4 DP. Consequent to discussions between the FDA and Juno on April 2, April 8, and May 1, 2020 and corresponding information requests sent on April 6, 2020 and May 11, 2020 the formulation process was adjusted to reduce excess volumes supplied to the clinical site. The final proposed formulation, provided in Amendment 44 (received on 05/26/2020), is reviewed below in the context of the negotiated commercial release criteria for (b) (4) (Amendment 38, received on 05/06/2020) that is used for dose determination (Table 89) and the upper dose range recommended by the clinical review team.

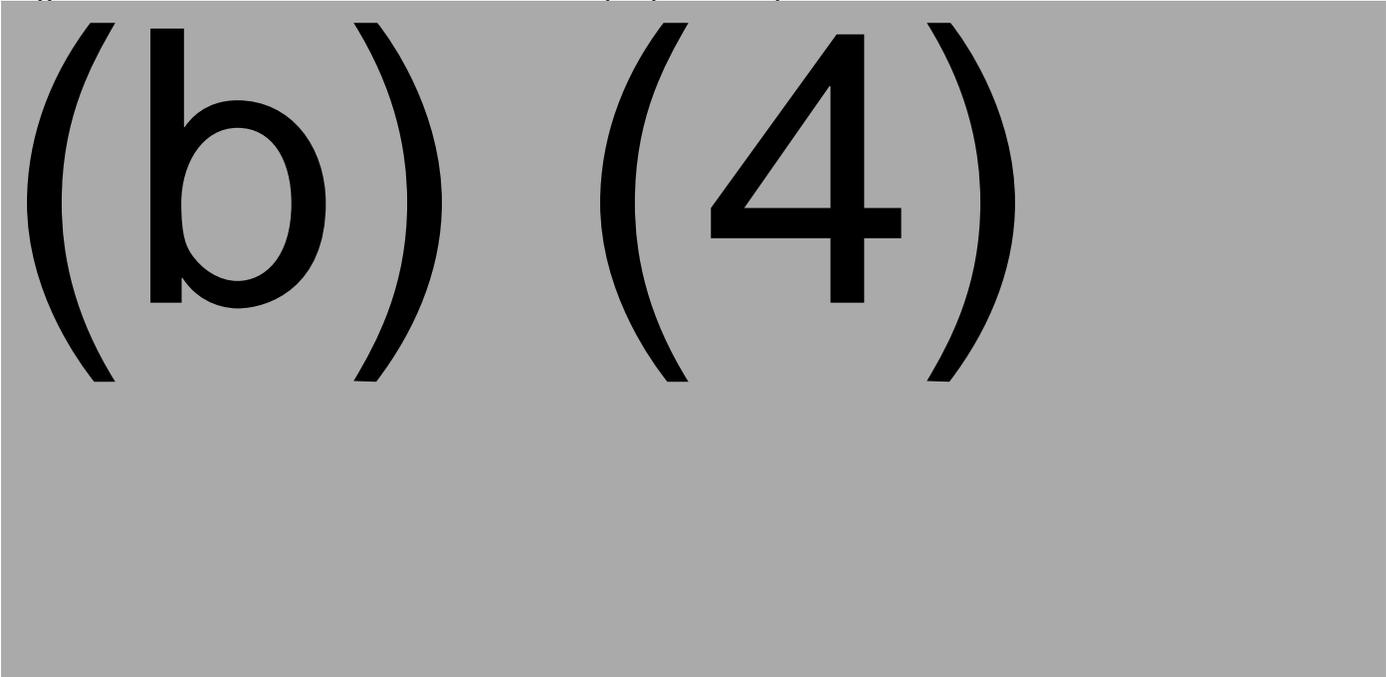
(b) (4)



Juno modeled the effect of the change with data from clinical manufacturing data that included a range of formulation targets, from (b) (4), to identify a formulation target that ensures that the majority of batches yield a target dose volume of at least (b) (4) while minimizing the magnitude of the change relative to clinical experience for DP (b) (4). The clinical manufacturing experience included formulation ranges for the CD8 DP from (b) (4) cells/mL and for the CD4 DP from (b) (4) of CD4 DP lots and (b) (4) of CD8 DP lots would fall within the modeled (b) (4) ranges

Reviewer comment: These calculations are based on proposed dose at the time of review: 100×10^6 CAR+ T cells (50×10^6 CAR+ cells per DP).

Figure 16 JCAR017 formulation and dose preparation process



Data provided in Amendment 30 (received on 04/14/2020) indicated that the (b) (4) post-thaw recovery is (b) (4), and the minimum observed in the clinical study was 39.5% recovery. To evaluate the predicted volume that will be delivered at various transduction rates, volume delivered at (b) (4) recovery when formulated with (b) (4) was calculated (Table 65). These calculations indicate that all lots with (b) (4) and with the (b) (4) post thaw recovery rate will require (b) (4) administered for each DP to meet the top dose level. In comparison,

(b) (4) of CD4 DP lots and (b) (4) of CD8 DP lots administered during clinical study 17001 had dose volumes of at least (b) (4). Importantly, with the new formulation calculation the entire intended dose of (b) (4)⁶ CAR T cells can be accommodated for a CD8 DP with worst-case manufacturing (b) (4) post thaw recovery and lowest commercial (b) (4).

Reviewer comment: This proposal considerably reduces the overfill and stays within the manufacturing experience during the clinical study. Importantly, the reduction in final cell concentration should not be substantial enough to affect DP release testing, I would be concerned about the impact on release testing if the concentration was changed by more than (b) (4).

(b) (4)

Reviewer comment: Juno's risk assessment to support the revised formulation strategy was based on the proposed target dose of 100×10^6 CAR+ cells. The clinical review team recommended an increased final dose range with an upper dose of 110×10^6 CAR+ cells, as compared to Juno's proposed 100×10^6 CAR+ cells, and consequently (b) (4) CAR+ cells per component as indicated in Table 65. The formulation review has focused on administration of the top of the dose range as the highest allowable dose is usually targeted for infusion, and is recommended in the PI. Although overfill is reduced, more than the intended dose may be shipped to the clinical site and therefore the concern for medical errors and over dosing remains.

Juno provided limited information in Amendment 30 (received on 04/14/2020) from (b) (4) lots indicating that the administered dose was consistent with the provided release for infusion instructions (b) (4). Additionally, no correlation was found between the number of total or transduced cells administered and AE severity.

Reviewer comment: The provided data indicates that the dose preparation during the clinical study was followed. The preparation instructions in the proposed package insert state that additional product should not be administered. It is possible that the under commercial conditions, the adherence may be less stringent. Clinical study 17001 included a higher dose of 150×10^6 CAR+ T cells and the clinical review indicates that the severity of AEs did not increase with higher dose. Together with the proposed

reduction of excess DP component shipped, concerns with the formulation configuration should be moderated.

The updated formulation target results in a (b) (4). The studies presented in sections 3.2.P.2.3 Manufacturing Process Development demonstrate that the formulation is capable of producing a stable product with (b) (4). Studies included evaluation of (b) (4) which is in line with the new formulation concentration of (b) (4). Formulation robustness studies, reviewed in section 3.2.P.2.2.3 Physicochemical and Biological Properties, evaluated CD4 DP (b) (4) for the CD8 DP during long term storage and indicate that the formulation can support the change. Although PPQ batches operated at the historical formulation target, (b) (4) of each CD8 and CD4 PPQ batches, were within the modeled range of DP concentrations for the updated harvest criteria. Therefore, Juno has concluded that the proposed change in formulation target is low risk and that DP quality attributes are not expected to be adversely impacted.

Reviewer comment: The change in formulation target is a (b) (4) and not the manufacturing process, therefore the process validation remains applicable. The manufacturing development and stability studies reviewed can be applied to the new formulation target because they included the new target concentration.

In-use stability:

Compatibility with the (b) (4) during thaw to administration: (b) (4)-derived CD8 and CD4 DPs, were thawed on the benchtop at RT according to the Product Insert (PI) instructions for up to (b) (4) hours; the individual thaw time was noted to be between (b) (4) minutes. At the indicated hold times, the DP was withdrawn from the (b) (4) vial using a 20-g needle into a syringe per the PI instructions. Cells were tested for (b) (4)

All parameters remained stable throughout the study indicating that the DP was stable regardless of cell concentration. The DP lots included cell concentrations representative of the updated (b) (4)

Reviewer comment: The original submission included data from (b) (4) DP lots, additional data for a (b) (4) DP lot was provided in Amendment 30 (received on 04/14/2020) and is included in the review. Acceptable.

The thawed DP is to be administered by infusion using standard intravenous access catheter and non-filtered tubing supplied by the clinical site. Compatibility studies with FDA cleared devices for venous access were not performed. JCAR017 is derived from leukapheresis material and therefore is compatible with devices cleared for transfusion of blood products. Juno performed compatibility studies to support the dose preparation procedure performed at the clinical site.

Compatibility with (b) (4) 20-gauge needle: A (b) (4) syringe with a 20- (b) (4) gauge needle was used to withdraw the DP from the vials for administration. Juno

evaluated (b) (4) and (b) (4) of (b) (4) DP lots. There was no statistical difference when using either size needle as determined by a (b) (4)

Reviewer comment: The PI indicates that a 20-gauge needle should be used during dose preparation. Acceptable.

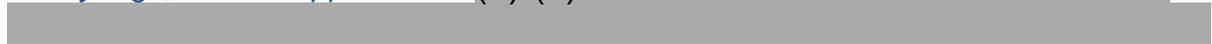
(b) (4)



(b) (4)



Reviewer comment: The provided data indicates that the DP is not stable over time in the syringe, with an approximate (b) (4)



syringe). The administration manual proposes allowing a 2 h (120 minute) limit from dose preparation to administration.

Juno provided additional data from a study evaluating DP compatibility with (b) (4) syringes. The study evaluated (b) (4) CD4 lots and (b) (4) CD8 lot with (b) (4) in a 5 mL syringe for up to (b) (4) as a worst-case scenario. This data indicates that there was no change in the (b) (4) or in the (b) (4) during the (b) (4) course when using a (b) (4) syringe. In contrast, (b) (4) was reduced by (b) (4) syringes and (b) (4) syringes.

Reviewer comment: It would be expected that the smaller volume in the 5 mL syringe would have a larger change, however this was not observed with the additional data. Together these studies indicate that the DP may be affected by different conditions during preparation. The allowable post hold time in the proposed PI (up to 2 h) is consistent with that allowed during the clinical study, however Juno did not collect data from the clinical site on the time held between thaw and administration. The logistics of dose preparation, delivery to the bedside, and infusion (0.5 mL/minute) are complicated and if rushed may lead to medical errors; the expiry time should be reasonable to allow product preparation and administration. The product administration is consistent with the clinical study and therefore any loss of product should be consistent with the administration history and clinical study experience. Overall, the studies indicate that (b) (4) of the product should be stable if administered within the 2 h timeframe. Acceptable.

The studies provided in the original BLA submission do not address two important parameters for dose administration:

1. The PI indicates that the vial should be mixed by inverting the vials, however there is no number of inversions indicated. Juno provided study data to support 5 inversions in Amendment 37 (received on 05/05/2020). Briefly, the study assessed the cell concentration after 5 inversions, defined as rotating the vial (b) (4), and then back (b) (4) to the starting upright position, across (b) (4) of (b) (4) filled (b) (4) vials (b) (4) total vials) after cryopreservation and thaw, including (b) (4) for the CD8+ and CD4+ DP lots. The average CV between the DP lot vials in these data is (b) (4) for the CD8 DP and (b) (4) for the CD4 DP; consistent with assay variability of (b) (4) CV. *Acceptable, "5 inversions" was added to the PI.*
2. Syringes usually retain a measurable volume after administration. Studies described in the original submission indicated that the cell concentration was consistent, however there was no confirmation that the administered volume and consequently the dose, was consistent. Juno provided data in Amendment 40 (Table 64) indicating that a consistent volume is delivered and that the residual syringe volume is less than (b) (4) and therefore should not affect the administered dose. *Acceptable.*

3.2.P.2.2.2 Overages

Reviewed by KLWS

There are no overages included in JCAR017.

3.2.P.2.2.3 Physicochemical and Biological Properties

Reviewed by NB

The physicochemical and biological properties of CD8 DP (b) (4) and are described in section 3.2.S.3.1 Elucidation of Structure and Other Characteristics of this BLA review.

3.2.P.2.3 Manufacturing Process Development

Manufacturing Process History and Comparability:

JCAR017 was manufactured by (b) (4) distinct processes during clinical development (Figure 18). Process (b) (4) was in the original IND submission and included (b) (4) of the final product through the (b) (4). The (b) (4) step resulted in (b) (4) final DP (b) (4) in development; no clinical data using (b) (4) is used to support this BLA. Manufacturing processes (b) (4) were used (b) (4)

Manufacturing process (b) (4) is consistent with the proposed commercial manufacturing process and 162 subjects in study 17001 received product produced from (b) (4). Prospective analytical comparability studies based on (b) (4) leukapheresis studies were reviewed during product development (July 2017) concluded that the processes were comparable. There was a significant improvement in final DP viability with the implementation of (b) (4) manufacturing, this was considered a process improvement and should be reflected in the commercial release criteria. Additionally, Juno conducted a retrospective comparability assessment of products produced by (b) (4) by comparing the effect size a subset of release testing (b) (4)

The retrospective assessment corroborated the prospective analytical comparability studies. Juno also provided the (b) (4) report to retrospectively compare efficacy, safety, and pharmacokinetics across manufacturing processes (b) (4) (see clinical review).

Reviewer comment: The comparability studies to support the pooling of clinical data generated using manufacturing processes (b) (4) were reviewed during the IND and were deemed acceptable.

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

(b) (4)

(b) (4)

Juno provided detailed information on process characterization studies and the correlation to product attributes (summarized in Table 68). The process characterization studies were used to evaluate commercial manufacturing process parameter ranges.

(b) (4)

(b) (4)

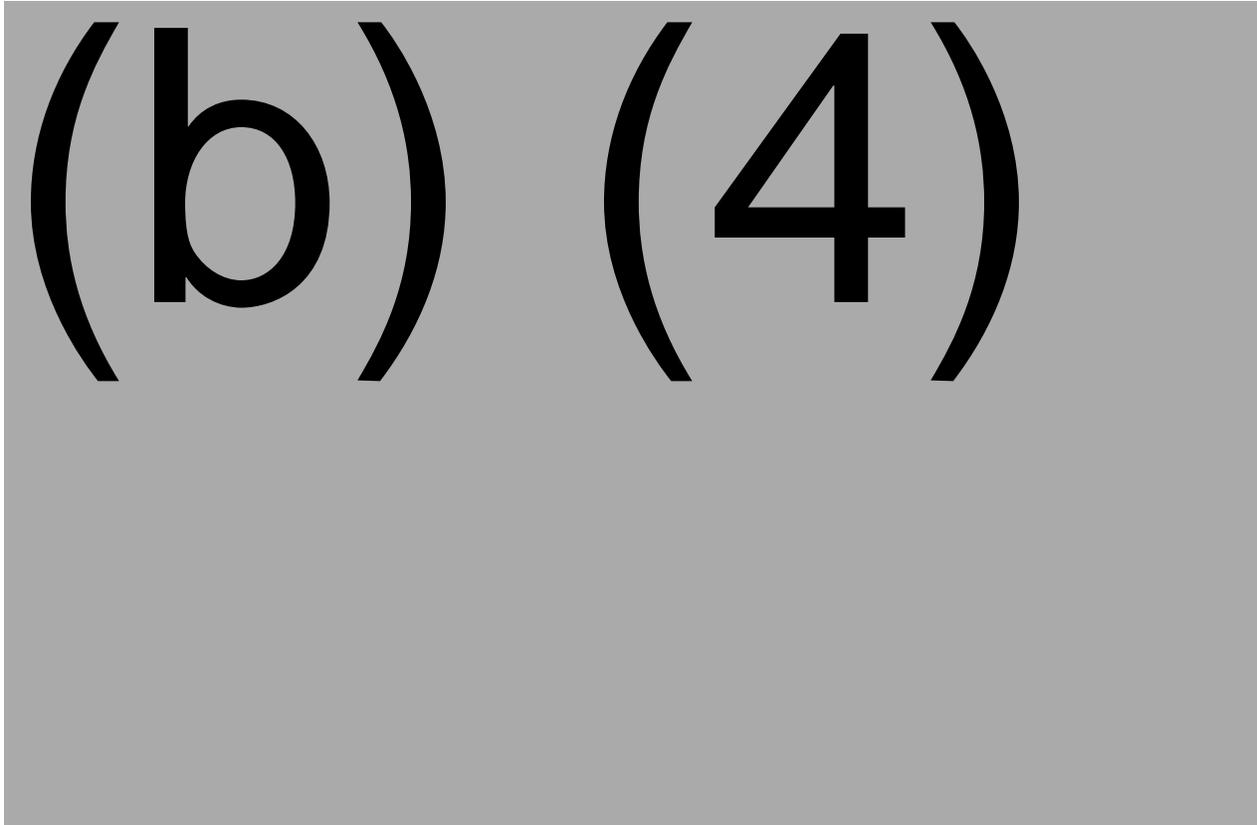
3 pages determined to be not releasable: (b)(4)

Reviewer comment: The characterization studies evaluated a variety of parameters and their effect on CQAs. The characterization studies further defined the parameter ranges that were experienced during clinical study. Historical data for CPPs and IPCs was submitted in Amendment 22 (received on 03/26/2020) and is included in the PPQ review.

The process characterization studies analyzed the product CQAs at each process step in the JCAR017 manufacturing process (Table 69).

(b) (4)

(b) (4)



Reviewer comment: The proposed criteria were met for every parameter during the process characterization studies. However, these criteria differ from the negotiated commercial release criteria. For example, at the time of the study, transduction efficiency was acceptable at (b) (4). Importantly, our evaluation indicates that the characterized parameters should support production of conforming product.

Commercial Manufacturing Process Control Strategy (PCS):

Impact of Raw Materials:

Juno conducted a risk assessment on raw material criticality using a weighted scoring methodology with (b) (4) categories: (b) (4)

(b) (4) The criticality assessment yielded a range of criticality scores from (b) (4) and a cutoff of (b) (4) was applied to classify raw materials as critical. Critical raw materials were determined to be the (b) (4)

(b) (4)

(b) (4)

Reviewer Comment: This analysis is informative, but with the following caveats:

- 1. The analysis indicates that all variation in the (b) (4) is due to leukapheresis variation. However, the variance is extremely low, (b) (4), for both the clinical and PPQ lots indicating that the CQA is tightly controlled with little overall variance. If there was a larger observed variance, it would likely be due to a failure in the selection process, and thus a variance in the process, rather than the incoming leukapheresis material as the historical experience with the selection process indicates it is highly reproducible across hundreds of patient production runs.*
- 2. The analytical variance from PPQ does not accurately reflect the analytical variance presented in the validation of analytical procedures. For example, the (b) (4) method validations indicate that the variance is low, but intermediate precision ranges from (b) (4) (b) (4) which correlate with the low CQA variance in in study (total variance of (b) (4))*

With the caveats noted, the PPQ paired run analysis suggests that a measurable amount of variability that is due to the variable leukapheresis as is generally expected for autologous products.

Impact of product quality attributes:

Juno conducted a risk assessment to determine the criticality of product attributes based on (1) the impact of the attribute on JCAR017 safety and efficacy (reviewed in 3.2.S.3.1 Elucidation of Structure and Other Characteristics) and (2) the level of understanding of the attribute as assessed by the uncertainty index. The uncertainty index is impacted by the range of data for that attribute from the clinical study (e.g., low uncertainty for (b) (4) because a wide range of values was tested during the study) and the amount of scientific knowledge pertaining to the attribute (e.g., uncertainty for sterility testing is low because the field has a high level of understanding of the impact of bacterial contamination). Attributes determined to be CQAs are tested for lot release, non-CQAs are not. Juno indicates that (b) (4)

(b) (4) will be continued for further product characterization but not for lot release.

(b) (4)

Reviewer comment: The negotiated commercial release criteria for (b) (4) is (b) (4), which adequately controls for exclusion of residual CD19+ cells in the DP.

(b) (4) were considered to be of low impact because of a lack of correlation with safety or efficacy, however the FDA did not agree

3.2.P.5 Control of Drug Product) and both are tested for lot release. *Acceptable.*

Process related impurities, including (b) (4) were assessed. All were classified as non-CQAs due to clinical study experience, toxicity knowledge, and exposure risk. The exposure limit for each is listed, as applicable.

Reviewer comment: (b) (4) were classified as non-CQAs but included as part of lot release testing (Table 89). Acceptable.

Integrated control strategy (ICS):

The ICS was developed, in accordance with the Celgene Global standard for CPV and based on experience with the proposed commercial process. Review of CQAs, CPPs, IPCs, and processing times was detailed with a report generated quarterly (at least (b) (4) lots). Additional details were provided in Amendment 57 (received on 07/21/2020).

3.2.P.2.4 Container Closure

The DP components are filled into 5 mL cryogenic (b) (4) vials (Table 70) and stored at -130°C. The vial has been used for manufacturing processes (b) (4). The vials are provided sterile via (b) (4) from (b) (4) and information is cross referenced to MF (b) (4). See section 3.2.P.7 Container Closure System for a full review. Biocompatibility has been established through the JCAR017 stability studies in section

3.2.P.8 Stability of this BLA review.

Table 70 DP Primary Packaging

Component	Description
Vial	5-mL cryogenic vial made of (b) (4)
Vent Port	(b) (4) tubing with PE microbial filter plug
Loading Port	(b) (4) tubing with a (b) (4) female luer lock and an (b) (4) closed male luer cap
Retrieval Port	(b) (4) septum covered with a polypropylene and aluminum flip-off cover

The (b) (4) is manufactured in accordance to ISO (b) (4). The body of the product vial is manufactured to meet the supplier's release specifications, which include compliance with the current edition of (b) (4)

Extractable and leachable studies, including forced extraction and leachable simulation studies, are reviewed in section 3.2.P.7 Container Closure System of this BLA review. In brief, no organic compounds or heavy metals were detected. (b) (4) elemental impurities were identified for the vial (b) (4) and (b) (4) for the tubing (b) (4). The only elemental impurity detected in the study was (b) (4). The evaluation provided by Juno concluded that the container closure system does not pose a risk for patient safety with regard to extractable compounds.

Container Closure integrity testing was conducted via (b) (4) was completed on a total of (b) (4) containers, each with a 5mL fill volume (reviewed by Rabia Ballica, OCBQ/DMPQ). Testing included storage at $\leq -130^{\circ}\text{C}$ for durations up to (b) (4), and shipment to a testing facility within an LN2 shipping container. Briefly, no concerns with ingress were observed.

3.2.P.2.5 Microbiological Attributes

The DP is aseptically manufactured and tested for sterility and endotoxin as a part of release testing. The (b) (4) are sterile (b) (4) by the vendor). Container-closure integrity testing using (b) (4) has demonstrated that the (b) (4) is an adequate barrier to prevent microbial contamination (reviewed by Rabia Ballica, OCBQ/DMPQ).

Reviewer comment: No concerns were identified.

3.2.P.2.6 Compatibility

Compatibility of the administration syringe is reviewed in section 3.2.P.2.2 Drug Product of this BLA review.

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

The original formulation process allowed for an excessive volume of the DP components above the intended dose to be delivered to the clinical site. The interactive review process detailed in the review, resulted in the proposal of a formulation that reduces overfill and is supported by data from the clinical manufacturing and development studies. Adequate data was provided to support the preparation and administration process described in the proposed package insert. A 2h limit is defined for the preparation and administration process.

Comparability studies support the inclusion of clinical data generated by product using manufacturing processes (b) (4) provided prospective analytical data and retrospective comparisons. Both evaluations support comparability. Prospective comparability studies support the change to (b) (4) to mitigate contamination risk. Juno conducted appropriately designed characterization studies to support the manufacturing process validation and define CPPs and IPCs.

3.2.P.3 Manufacture

Reviewed by KLWS

3.2.P.3.1 Manufacturer(s)

Table 71 JCAR017 DP Manufacturers

Site	Registration	Address	Function
Juno Therapeutics Inc., Manufacturing Plant	FEI: 3011834594 DUNS: 079941307	1522 217th Pl. SE Bothell WA 98021 United States	DP manufacturing Primary and secondary packaging DP release and stability testing

(b) (4)

3.2.P.3.2 Batch Formula

A batch is defined as (b) (4) of DP. The batch provides enough cells for the DP formulation and the QC testing and retains.

Table 72 JCAR017 Batch Formula

Ingredients	Quality Standard	Amount per batch	Concentration
JCAR017 CD8+ cells	(b) (4)	(b) (4)	≥1.5x10 ⁶ CAR+ viable T cells/mL
CryoStor CS10 (contains (b) (4) DMSO)	(b) (4)	(b) (4)	75% [v/v]
Multiple Electrolytes Injection, Type 1	(b) (4)	(b) (4)	(b) (4) [v/v]
Albumin (Human) Solution (25% Albumin)	(b) (4)	(b) (4)	(b) (4) [v/v]

UNII code: 7K2YOJ14X0

a Final DMSO concentration in the drug product is 7.5%

b Final albumin concentration in the drug product is (b) (4)

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

The DP is manufactured at the JuMP facility in Bothell, WA. Each DP lot targets up to (b) (4) total of the (b) (4). Information provided is acceptable, with no deficiencies identified.

3.2.P.3.3 Description of Manufacturing Process

The JCAR017 DP manufacturing process consists of a (b) (4) followed by formulation. Formulated DP is aseptically filled into four DP vials and cryopreserved for storage at ≤-130°C. Reprocessing of the DP is not allowed. Although the CD4 and CD8 DP components are manufactured separately, the process and controls are identical. Chain of identity procedures and batch scale are described in 3.2.S.2.2 Description of Manufacturing Process.

Figure 20 JCAR017 DP manufacturing flow chart



Description of the manufacturing process:

The final formulation process was (b) (4) cells submitted in Amendment 44 (received on 05/26/2020). The change in formulation to reduce overfill is reviewed in section 3.2.P.2.2.1 Formulation Development.

(b) (4)

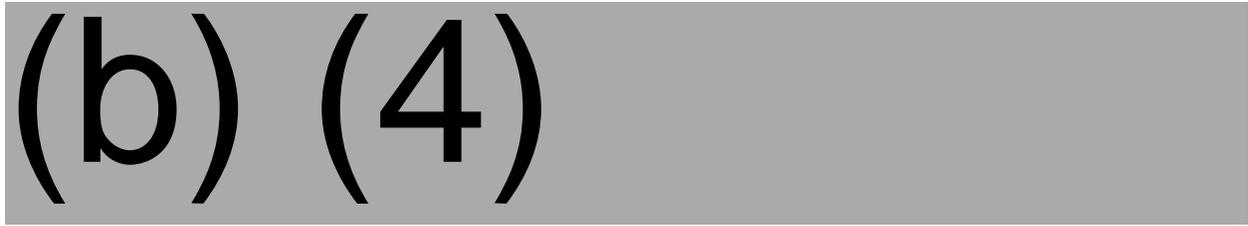


Overall Reviewer’s Assessment of Section 3.2.P.3.3:
The JCAR017 DP formulation, filling, and cryopreservation processes are acceptable. No deficiencies were identified.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Table 73 DP CPP

(b) (4)



There are no IPCs for the DP manufacturing process. The last DS IPC (Table 59) controls the number of cells required for harvest. Processing times are defined through the packaging and shipping procedures (additional information provided in Amendment 44, received on 05/26/2020).

(b) (4)



Overall Reviewer's Assessment of Section 3.2.P.3.4:

The JCAR017 DP manufacturing process and controls are appropriate to ensure product quality, with no deficiencies identified.

3.2.P.3.5 Process Validation and/or Evaluation

Process characterization and the process risk assessment are reviewed in section 3.2.P.2.3 Manufacturing Process Development of this BLA review.

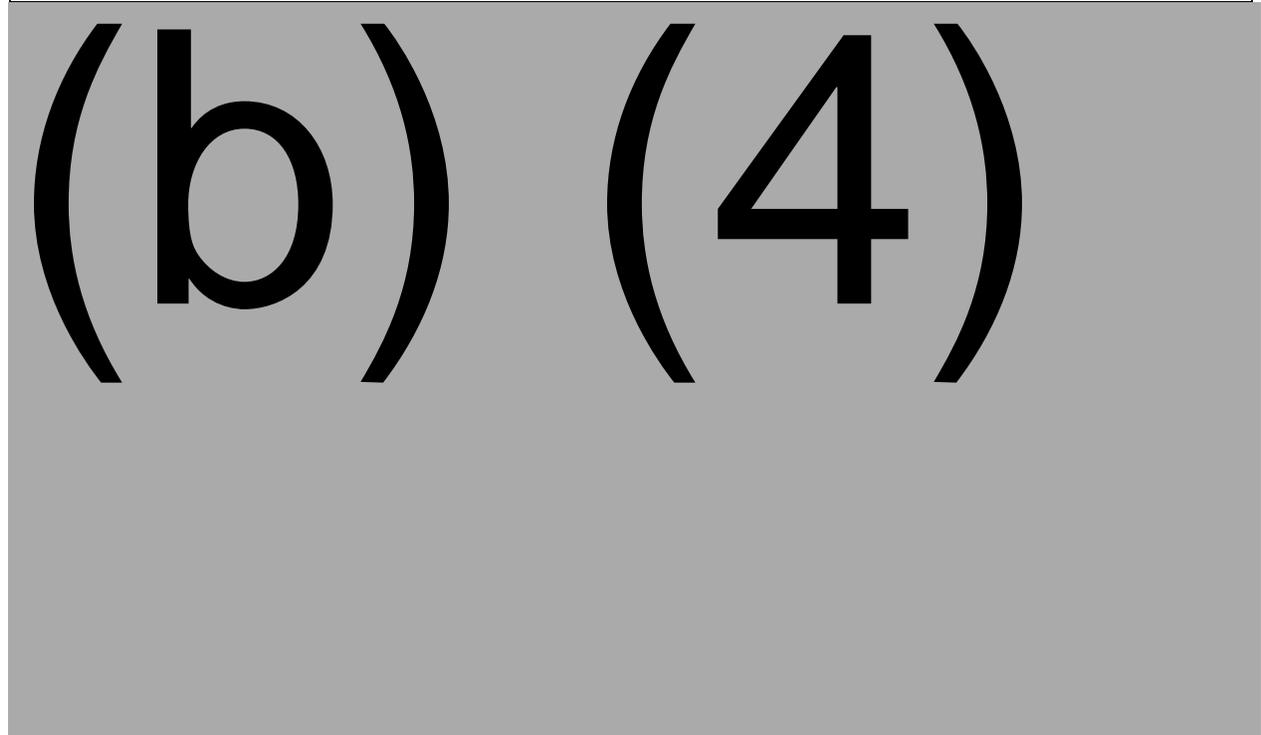
(b) (4)



(b) (4)



(b) (4)



(b) (4)



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

Process Performance Qualification (PPQ):

The PPQ for the CD8 and CD4 DPs were reported as one study and is representative of the proposed manufacturing process at the scale and facility intended for commercial production. RPT-001861 details the results of the JCAR017 PPQ study that was conducted at the JuMP facility with the current Master Batch Records and was provided in Amendment 6 (received on 01/27/2020). Testing was performed using validated methods. (b) (4)

(b) (4) effective at the time and based on the clinical manufacturing data to date. Following completion of the PPQ campaign, the PCS was updated to (b) (4) based on additional process knowledge gained during the PPQ manufacturing runs and completion of further process characterization studies. The PPQ studies were consistent with PCS (b) (4) expectations.

(b) (4)

The PPQ summary provided in the BLA original submission was not the full PPQ report and did not include additional in-process testing results. For example, data pertaining to (b) (4) of the leukapheresis material (b) (4) was not provided. Juno provided additional data in Amendment 6 (received on 01/27/2020) and 17 (received on 03/10/2020). Of note, the (b) (4) parameters were considered exploratory and not compared to predefined acceptance criteria. Tables and graphs included in the Process Validation review were generated by the FDA to summarize Juno data when appropriate.

(b) (4)

(b) (4)

The leukapheresis material is shipped fresh to the manufacturing site. The PPQ material shipments met the shipping requirements with temperatures maintained between (b) (4). The leukapheresis material met established IPCs before selection for lisocabtagene manufacturing (Table 76). The thawed, selected material must meet a minimum number of (b) (4) prior to forward processing through the manufacturing process and the selection step is controlled by CPPs. All CPPs and IPCs were met.

(b) (4)

(b) (4)

There were less CPPs and IPCs for the clinical manufacturing process at the time of the PPQ than proposed for the commercial process. Comparisons indicate that the ranges observed during the PPQ were similar to those observed with the clinical (b) (4) manufacturing process (Table 77).

(b) (4)

(b) (4)

Reviewer comment: The leukapheresis collection volume was based on the shipping validation. However, the lower limit is well below the PPQ and clinical experience. Juno justified this limit by indicating that the cellular starting material parameters are defined for the selected material. Acceptable.

The efficiency of the selection step was determined by comparing (b) (4) data from the leukapheresis starting material to the CD8+ and CD4+ selected (b) (4) plots for starting materials and in-process samples are generated from a

qualified method used for characterization of process intermediates. The (b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

(b) (4)

[Redacted]

[Redacted]

(b) (4)

3.2.P.5 Control of Drug Product. The FDA suggested that an IPC be included to monitor the selection process as reviewed in section 3.2.S.2.4 Controls of Critical Steps and Intermediates of this BLA review.

All CPPs were met for all lots (Table 80). (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

PPQ lot release testing was conducted according to the proposed commercial release criteria (Table 82). The PPQ study included testing for Identity, Mycoplasma, (b) (4) (b) (4) testing; all lots passed. All lots passed appearance testing and were described as 'opaque, slightly yellow'.

(b) (4)

(b) (4)

(b) (4)

The individual CQA results are consistent with the experience for clinical trial lots that were manufactured with the proposed commercial process (b) (4). Importantly, the PPQ runs and the historical data indicates that B cells are effectively excluded from the DP.

Reviewer comment: The PPQ CQAs were analyzed according to the release criteria in the BLA OS. The PPQ runs all pass the commercial release criteria negotiated during the BLA review (Table 89).

Additional testing was performed on the PPQ lots to further characterize the T cell attributes (Figure 23). This data indicated that the PPQ DP lots contained polyfunctional CAR T cells, as measured by (b) (4) which is indicative T cell persistence and antitumor activity.

(b) (4)

(b) (4)

Reviewer comment: When analyzing the PPQ lots, (b) (4) were good correlates to CAR frequency for the CD8 DP (Figure 23). For the CD4 DP, (b) (4) correlated less with (b) (4). The analysis is limited in the small range of (b) (4) observed across the PPQ lots. No concerns were identified.

T cell subsets in the final PPQ DP lots were characterized (Table 83). The manufacturing process had little influence on the T cell subsets for the CD4 DP, (b) (4) were already highly expressed on the CMAT cells. For the CD8 DP, the (b) (4) as compared to the CMAT composition, which reduces the immediate effector cell activity. Additionally, the overall levels of (b) (4). These profiles were correlated with increased pharmacokinetics and decreased clinical safety events in exploratory studies.

(b) (4)

(b) (4)

Process related impurities: Impurity removal is contingent on (b) (4) steps during the manufacturing process. All impurities were removed below the predefined acceptance criteria, often magnitudes below the required level, during the PPQ study (Table 84).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

COI/COC Validation: Procedures to maintain the COI and COC are reviewed in Control of Starting (i.e., Source) Material(s) and 3.2.A.1 Facilities and Equipment of this BLA review. The process was prospectively validated during the PPQ runs by demonstration of control from leukapheresis collection to product release. Retrospective analysis indicates that the COI and COC procedures in place have been sufficient throughout the clinical study with limited COI or COC product mix-ups. Descriptions of COI/COC-related deviations were provided in Amendment 60 (received on 08/4/2020).

There were 7 incidents related to disruption of the COI/COC during the clinical study. In each case, similar errors have not occurred since corrective actions were implemented.

- 2 incidents in 2018 pertained to addition of (b) (4) from the same patient. The second incident occurred prior to CAPA implementation, in both cases the manufacturing was terminated. The investigation indicated that the controls (e.g., labeling was correct) functioned as expected and the root cause was operator error.

- 3 incidents that occurred within a 45 day period in 2019 were related to test sample mix ups: 2 incidents pertained to (b) (4) the CD4 and CD8^{(b) (4)} samples, which was revealed by the (b) (4); 1 incident pertained to a mix up between the test sample and the (b) (4) (b) (4) for the (b) (4) determination. The mix ups were determined to have occurred during sample preparation as the QC test sample tubes were correctly labelled. The corrective actions require COI to be maintained through the analytical protocol through increased check points.
- 1 incident in 2018 resulted from two shipments of JCAR017 that were inadvertently switched by the (b) (4) handler upon delivery of two dewars to the (b) (4) for transport. Consequently, the products were shipped to the incorrect site where the mix up was discovered during identity check at the clinical site. Both lots were returned to the JuMP facility and disposed of. Corrective actions include (b) (4) per courier at a time.
- 1 incident in 2019 resulted from the courier picking up an empty dewar instead of the dewar containing JCAR017. The incident was identified while the courier was en route to the (b) (4) and the courier returned to retrieve the correct dewar. The investigation indicated that the courier did not follow proper COI verification when picking up the dewar including sign off by Juno personnel. Corrective actions include updated SOPs and training for the courier service and the removal of this employee from Juno deliveries.

Reviewer comment: The implemented corrective actions have abrogated repeat deviations and strengthened the COI/COC process.

Validation of Process Solution Preparation: Formulation consistency and uniformity was evaluated with prospective acceptance criteria to determine if in-process solutions can be manufactured as a consistent, homogenous solution. Consistency was demonstrated across three independent lots.

Reviewer comment: All predefined criteria were met with low variance. Acceptable.

(b) (4)

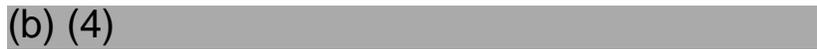
Extractable and Leachable Risk Assessment:

The final DP container closure extractable and leachable (E&L) profile is reviewed in sections 3.2.P.2.4 Container Closure and 3.2.P.7 Container Closure System.

(b) (4)



(b) (4)



(b) (4)

Impurity testing indicates that there is a (b) (4) reduction in substances introduced in the DS stage. Therefore, the compounds detected in the DS-contact material will be reduced below levels of concern. Reported no effect levels are well above the amount extracted.

Reviewer comment: The in-process E&L assessment is sufficient.

Shipping Validation:

The cryopreserved JCAR017 is shipped from JuMP to the infusion site in a temperature-controlled cryoport liquid nitrogen dry vapor shipper (LN2 Shipper) described in section 3.2.P.7 Container Closure System of this BLA review. The selected shipper is an off-the-shelf, dry vapor Dewar designed to maintain internal temperatures of (b) (4). Juno conducted a shipper validation study to support (b) (4) to account for the maximum expected hold times.

A total of (b) (4) were used for each set of testing (e.g., (b) (4)



(b) (4)



Reviewer comment: The provided data indicates that the shipper is adequate to sustain the indicated temperature to maintain a frozen DP during shipping. Use of surrogate material is not ideal for shipper validation studies, however can be used in combination with stability studies and accurate temperature logging. Discussions with Rabia Ballica (OCBQ/DMPQ) indicates that the testing was conducted appropriately to determine if the shipper is adequate to maintain physical and temperature integrity, however the studies would not evaluate the effect on the DP CQAs. Juno indicated that the stressed stability studies reviewed in section 3.2.P.8 Stability in conjunction with temperature maintenance indicate that the shipper is appropriately qualified. Additionally, the commercial shipping configuration has been successfully used for the clinical study. As JCAR017 should be maintained in a frozen state, it is not expected that the cells would be subjected to additional physical stress as would be possible if shipped in the liquid state. Therefore, the study is adequate to support the proposed shipping configuration.

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

The process validation provided is acceptable and demonstrates that JCAR017 can be consistently manufactured within the target operating ranges and meet the necessary CPPs, IPCs, and CQAs. Characterization studies indicate that the manufacturing process (b) (4). Additionally, impurities are reduced to adequate levels through the manufacturing process. Qualification of buffer and media production indicates that the processes are adequately controlled.

The original submission did not contain sufficient information to support process validation. Additional information was provided in Amendments 6 (received on 01/27/2020), Amendment 17 (received 3/10/2020), Amendment 30 (received on 04/14/2020), and Amendment 60 (received on 08/04/2020). The totality of information was adequate to demonstrate that Juno has appropriate control over the manufacturing process.

3.2.P.4 Control of Excipients

Reviewed by NB

3.2.P.4.1 Specifications

Excipients used in the formulation of CD4 and CD8 DPs are listed in Table 87 and CoAs were provided in the BLA.

Table 87 Excipients present in the CD4 and CD8 DPs

Reagent	Vendors/Suppliers	Quality Standard
CryoStor CS10	(b) (4)	Non-Compendial
Albumin (Human) 25%	(b) (4)	(b) (4)
(b) (4) (Multiple Electrolytes Injection, Type 1)	(b) (4)	(b) (4)

Non-compendial excipient CryoStor CS10 is released for use by Juno based on manufacturer testing and in-house testing results. CryoStor CS10 information is cross-referenced to BB-MF-(b) (4) and LOA is provided. CS10 release tests, methods and acceptance criteria are listed below (Table 88).

(b) (4)

(b) (4)

(b) (4)

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

Human Albumin (25%) and Multiple Electrolytes Injection, Type 1:

These are FDA-approved licensed products and the analytical procedures used to test the (b) (4) excipients comply with the current analytical procedures described in the (b) (4) *Acceptable.*

CryoStor CS10:

Manufacturer testing: The manufacturer's release testing procedures and validation of analytical procedure for CryoStor® CS10 is cross-referenced with master file, BB-MF-(b) (4). *In house testing: In response to Amendment 49 (received on 06/16/2020), Juno provided SOPs and validation/verification reports for in-house test methods discussed below. Acceptable.*

(b) (4)

(b) (4)

(b) (4)

CryoStor CS10. (b) (4)

. *Acceptable.*

3.2.P.4.4 Justification of Specifications

The specifications for the (b) (4) excipients are the same as those in the current (b) (4) chapters, and thus provide adequate control for use in the manufacture of JCAR017. CryoStor CS10 manufacturer testing procedures, methods and justification are described in the BB-MF-(b) (4). Juno has also evaluated the manufacturer’s procedure and specifications for CS10 lot release and performs additional testing and has established appropriate specification. *Acceptable.*

3.2.P.4.5 Excipients of Human or Animal Origin

The following excipients containing materials of human or animal origin are used:

1. Human Albumin (human plasma derived) is an FDA approved licensed product with marketing authorization in both US and EU. No issues.
2. CryoStor® CS10 (cryopreservation media) contains (b) (4)



Additional information is provided in section 3.2.A.2 Adventitious Agents Safety Evaluation of this BLA review.

3.2.P.4.6 Novel Excipient

There are no novel excipients used in the manufacture of JCAR017 drug product.

Overall Reviewer’s Assessment of Section 3.2.P.4:

The information on excipients and control of excipients provided by Juno in the original BLA and subsequent amendments as noted above is acceptable.

3.2.P.5 Control of Drug Product

Reviewed by NB

3.2.P.5.1 Specification(s)

The specification for the CD8 DP and CD4 DP is provided below (Table 89).

Table 89 Specifications for CD8 DP and CD4 DP

Quality Parameter	Attribute	Sampling Point	Analytical Test	Acceptance Criteria CD8+ DP	Acceptance Criteria CD4+ DP
Appearance	Color	Cryopreserved DP ($\leq -130^{\circ}\text{C}$), Post Thaw	Visual inspection (b) (4)	Colorless to Yellow or Brownish-Yellow, (b) (4)	Colorless to Yellow or Brownish-Yellow, (b) (4)
	Clarity			Slightly- ^{(b) (4)} Opaque	Slightly- ^{(b) (4)} Opaque
Identity	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purity	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Strength	(b) (4)	Cryopreserved (b) (4)	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Safety	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Sterility	(b) (4)	(b) (4)	No Growth	No Growth

	Mycoplasma	(b) (4)	(b) (4)	Not Detected	Not Detected
	Endotoxin	(b) (4)	(b) (4)	(b) (4)	(b) (4)

3.2.P.5.6 Justification of Specification(s)

CD8 and CD4 DP specifications were selected based on risk assessments that considered product understanding and process capability. The analytical procedures in the proposed commercial specification were selected based on their performance characteristics and suitability for routine and reliable evaluation of these attributes in a quality control environment. To establish commercial specifications, lots manufactured using the commercial process (b) (4) were used.

Data Analysis: (b) (4)

[Redacted]

Reviewer comment: The statistical method and analysis were verified by FDA's biostatisticians (Cong Wang and Zhenzhen Xu CBER/OBE).

The FDA review team and Juno discussed DP acceptance criteria multiple times during the review period. In IR#27 (sent 03/26/2020), Juno was informed that establishing acceptance criteria based on (b) (4) (initially proposed in the BLA) results in a wider range that is not supported by their clinical experience. Juno requested a teleconference to discuss commercial acceptance criteria. During a teleconference on 03/30/2020, Juno provided data analysis at (b) (4) and stated that acceptance criteria based on (b) (4) would be too stringent and result into failing (b) (4) lots manufactured using the commercial process (b) (4) that was found to be safe and effective in the clinical study 17001. FDA insisted that their original proposal of (b) (4) is not supported by their clinical experience. In Amendment 30 (received on 04/14/2020), Juno provided mean and standard deviation of conforming (b) (4) lots that were used to calculate (b) (4) (b) (4) FDA's biostatisticians (Cong Wang and Zhenzhen Xu) re-analyzed the data to confirm sponsor's assessment and were able to confirm sponsor's results. In Amendment 51 (received on 04/24/2020), Juno provided additional analysis of data obtained from (b) (4) lots at (b) (4) (b) (4). After analysis of all

the data submitted by Juno, in IR#42 (sent on 04/29/2020), FDA recommended to establish acceptance criteria based on (b) (4). In response to IR#42, Juno requested a teleconference (05/01/2020), where they presented data from other studies that were not included in the BLA to support acceptance criteria wider than the (b) (4). Juno was informed that since the new data is not part of the BLA and has not been reviewed, it cannot be used to support acceptance criteria for commercial product release to treat DLBCL patients. FDA re-iterated the lack of clinical experience with product CQAs outside the (b) (4). In Amendment 38 (received on 05/06/2020), Juno agreed to FDA's recommendation to establish commercial acceptance criteria for CD4 and CD8 DPs based on (b) (4).

Appearance: Performed on the final cryopreserved DP after thawing.

- **Color:** The color acceptance criterion for release and stability of both CD8 and CD4 DPs are 'Colorless to Yellow or Brownish-Yellow' (b) (4). Acceptance criteria were based on the analysis of data acquired during clinical development. All results for the CD8 and CD4 DP lots manufactured with the proposed commercial process were within the range (b) (4).
- **Clarity:** The clarity acceptance for release and stability of both CD8+ and CD4 DPs are 'Slightly-Opaque (b) (4)'. All tested CD8+ and CD4 DP lots manufactured with the proposed commercial process using patient leukapheresis were 'Opaque'. *Reviewer comment: The qualitative attributes of Color and Clarity were excluded from the statistical-based analysis for establishing acceptance criteria. This is acceptable.*

Identity: Identity testing is performed on the final DP after thawing. The identity acceptance criterion for release of both CD8 and CD4 DPs is (b) (4)

All tested CD8 and CD4 DP lots manufactured using the proposed commercial process met this acceptance criterion.

Reviewer comment: Currently, JuMP manufactures one type of anti-CD19 CAR T cell product (JCAR017). In addition to testing for (b) (4), Juno also test DP for CD8 and CD4 (b) (4), which also ensures identity of individual DP lots. In Amendment 28 (received on 04/09/2020), Juno changed the acceptance criterion from (b) (4). Acceptable.

Purity: Purity testing is performed on the final DP after thawing.

- (b) (4): The originally proposed (b) (4) acceptance criterion for release of both CD8 and CD4 DP was (b) (4) based on statistical analysis of (b) (4) lots manufactured using the commercial process (b) (4) and evaluated using the commercial procedure for (b) (4) and assay measurement uncertainty calculations. The majority of lots had (b) (4) level below the limit of detection of the assay (b) (4) and were not included in the statistical analysis. This was unacceptable.

Reviewer comment: After multiple rounds of communication, Juno agreed to establish acceptance criterion of (b) (4) based on (b) (4) and clinical experience. The (b) (4) upper limit was (b) (4) for CD8 DP and (b) (4) for CD4 DP (Figure 24). The (b) (4) based on clinical study experience. Acceptable.

(b) (4)

(b) (4)

- (b) (4)

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

(b) (4)

(b) (4)

Strength (b) (4)): Strength is assessed on the (b) (4)

Reviewer comment: In the original BLA, Juno proposed strength acceptance criterion for each DP (b) (4)

During BLA review, the clinical team did not agree to this proposed minimum dose, and the dose was (b) (4)

(b) (4) . Juno established a strength acceptance criterion for each component to meet the minimum dose in Amendment 80 (received on 10/27/2020).

(b) (4)

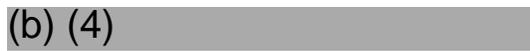
(b) (4)

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

(b) (4)



(b) (4)



(b) (4)

Potency (b) (4)

Potency is measured in cryopreserved products

(b) (4)





(b) (4)

(b) (4)

(b) (4)

Sterility: Sterility testing is performed on final formulated drug product (b) (4). The acceptance criterion for release is “No Growth”. [Acceptable.](#)

Mycoplasma: Mycoplasma testing is performed on drug product (b) (4) (b) (4). The acceptance criterion for release “Not Detected”. [Acceptable.](#)

Endotoxin: Endotoxin testing is performed on (b) (4). The acceptance criterion for release of both DPs is (b) (4).
Reviewer comment: There are two DPs in a single dose and up to (b) (4) of each DP can be administered. Thus, the maximum of (b) (4) can be administered per patient. At this volume, a maximum of (b) (4) can be administered. In worst-case-scenario, all the drug product containing (b) (4) endotoxin can be administered within 1 hour.

Sponsor justifies this by stating that since weight of an average adult is >60 kg, thus, the maximum dose of endotoxin administered will be (b) (4). This acceptance criterion ensures the maximum recommended dose of (b) (4) is not exceeded. At this acceptance criterion, if a patient with body weight up to 29.44 kg is administered the maximum volume of DP (b) (4) containing maximum level of endotoxin (b) (4) in 1 hour, the endotoxin level will be (b) (4). Clinical review team was consulted on this, and they did not have any concerns with this acceptance criterion. This is acceptable.

Justification for Attributes Not Included in the Specification:

Replication Competent Lentivirus (RCL) Testing: Testing for the presence of RCL in the final drug final is not included in the commercial specification. Juno states that the (b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

In the original BLA, CD8 and CD4 DP release specifications and justification provided by Juno was not acceptable. After interactive review, as described in detail above in the review, Juno established an acceptable commercial specification for both CD4 and CD8 DPs. No further issues.

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

Reviewer comment: All validation tables in this review were generated by the FDA from the assay validation reports provided by Juno.

Appearance

Procedure: Testing is performed using (b) (4)

. Juno has established quality control that ensures inspector trainings and

documentation. DP vials are (b) (4)

[Redacted]

(b) (4)

[Redacted]

[Redacted]

Reviewer comment: The SOP (MET-001013) was provided in Amendment 51 (received on 04/24/2020). Acceptable.

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

In Amendment 44 (received on 05/26/2020), Juno provided a copy of SOP-001030 (Qualification and Trend Analysis of Assay Controls) that details the number of assays to be executed and application of statistical analysis to establish control ranges or limits. Before the control lot is used in the test method, a qualification package is assembled, reviewed and approved per SOP-001030. For an assay to be valid, the results must be within the preliminary ranges. A minimum of (b) (4) results from independent, valid assays, including the results from the preliminary range calculation will be required to determine final ranges. This is acceptable.

(b) (4)



Reviewer comment: In Amendment 17 (received on March 10, 2020), Juno provided detailed information on assay controls, instrument calibration and controls, and procedures for qualification of (b) (4). SOP-000253 (qualification procedure for new lots of (b) (4), SOP-000166 (operation and maintenance of (b) (4)) and WIN-001062 (b) (4) procedure) were provided. This information was also reviewed by Heba Degheidy (OTAT/DCGT). Acceptable.

(b) (4)

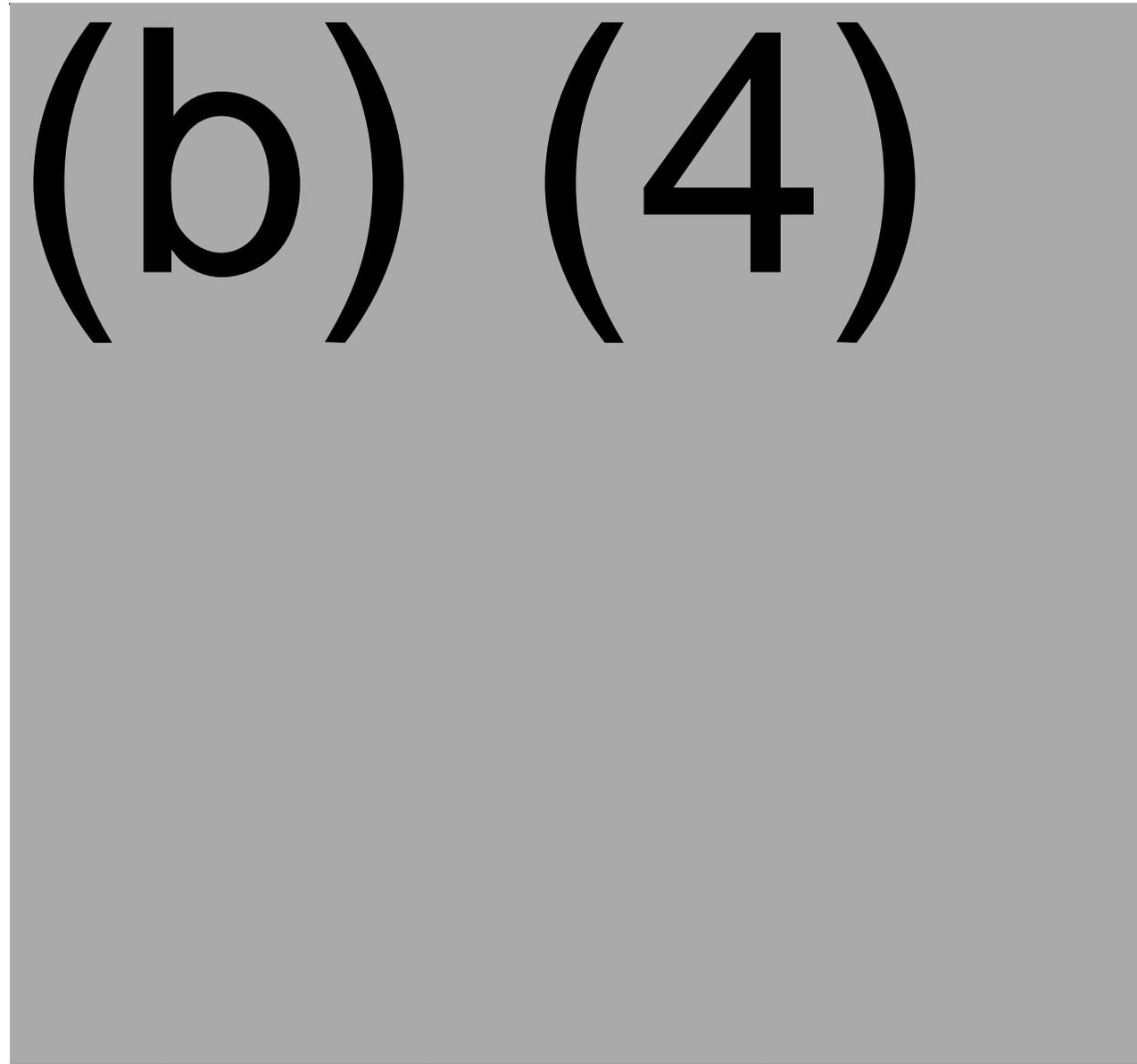


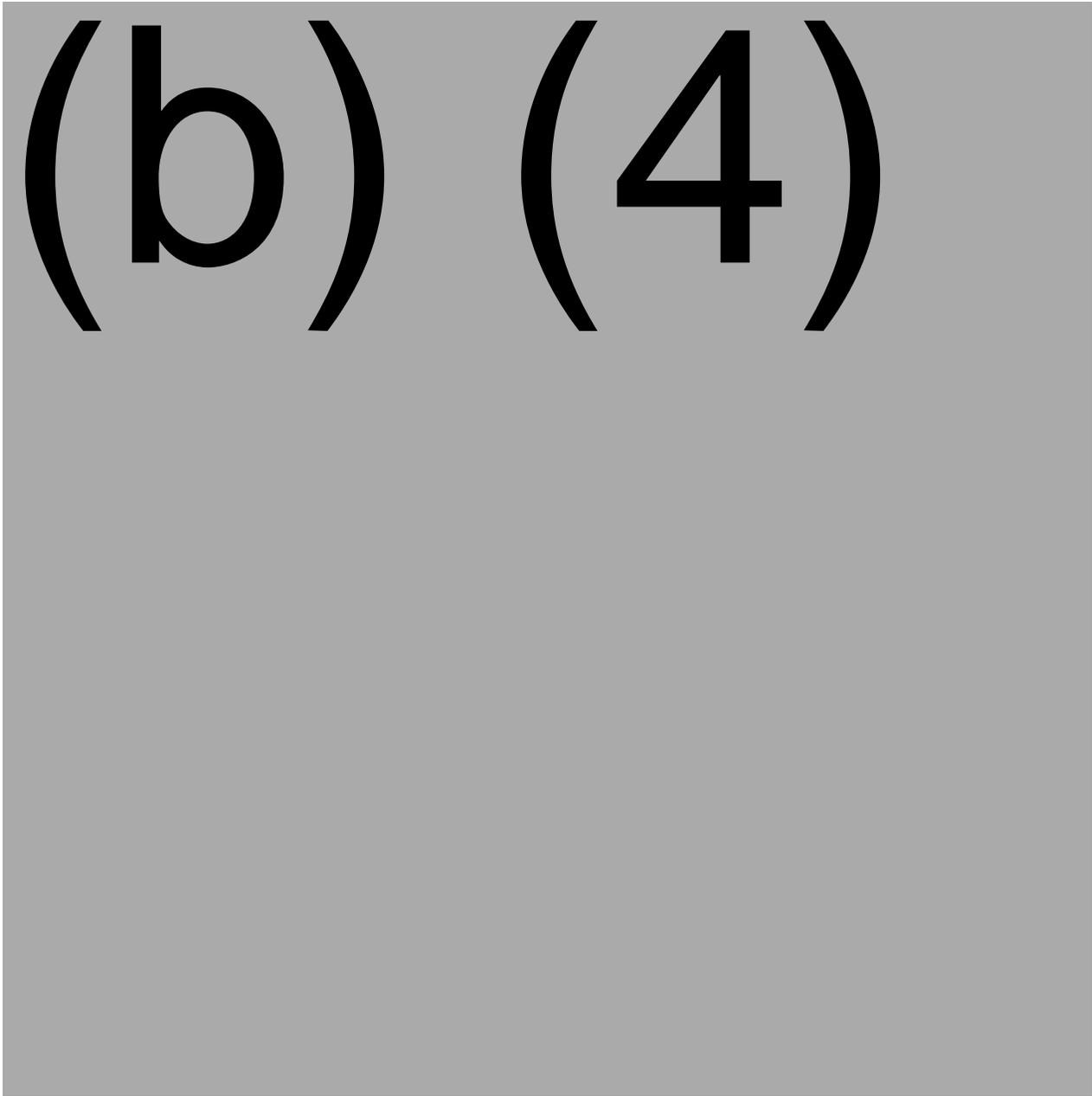
have acceptance criteria in the commercial specification (Table 90). The assay validation reports (RPT-001322 and RPT-001692) were provided in the BLA. CD4 and CD8 DPs were used for validation.

Reviewer comment: During review of the (b) (4) validation report, it was identified that sponsor had not provided validation information on (b) (4)

that were used in the study. Notably, the report only included specificity studies for the (b) (4). In Amendment 11 (received on 02/20/2020), Juno provided additional data on validation of each (b) (4). Acceptable.

(b) (4)





Reviewer comment: The (b) (4) method validation study used CD4 and CD8 DP lots and results met all the pre-established acceptance criteria and was demonstrated to be validated and fit for its intended purpose. Acceptable.



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

(b) (4)

(b) (4)

Endotoxin: The level of endotoxin present in the JCAR017 was assessed using (b) (4) as described in (b) (4)

Procedure: The level of endotoxin present in the JCAR017 was assessed according to (b) (4) as described in (b) (4). This (b) (4) assay is performed according to the test method (b) (4).

Verification: A verification was performed using (b) (4) lots of JCAR017 CD4+ and CD8+ DPs. The verification report (RPT-0396) was submitted to the BLA.

Reviewer comment: Review of the endotoxin detection method and verification was conducted by DBSQC. The review concluded that the endotoxin assay was qualified in accordance with (b) (4) and is suitable under the actual condition of use.

Overall Reviewer’s Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:
 The analytical methods and the validation of the analytical methods are acceptable. Validation data was obtained using JCAR017 DP as appropriate.

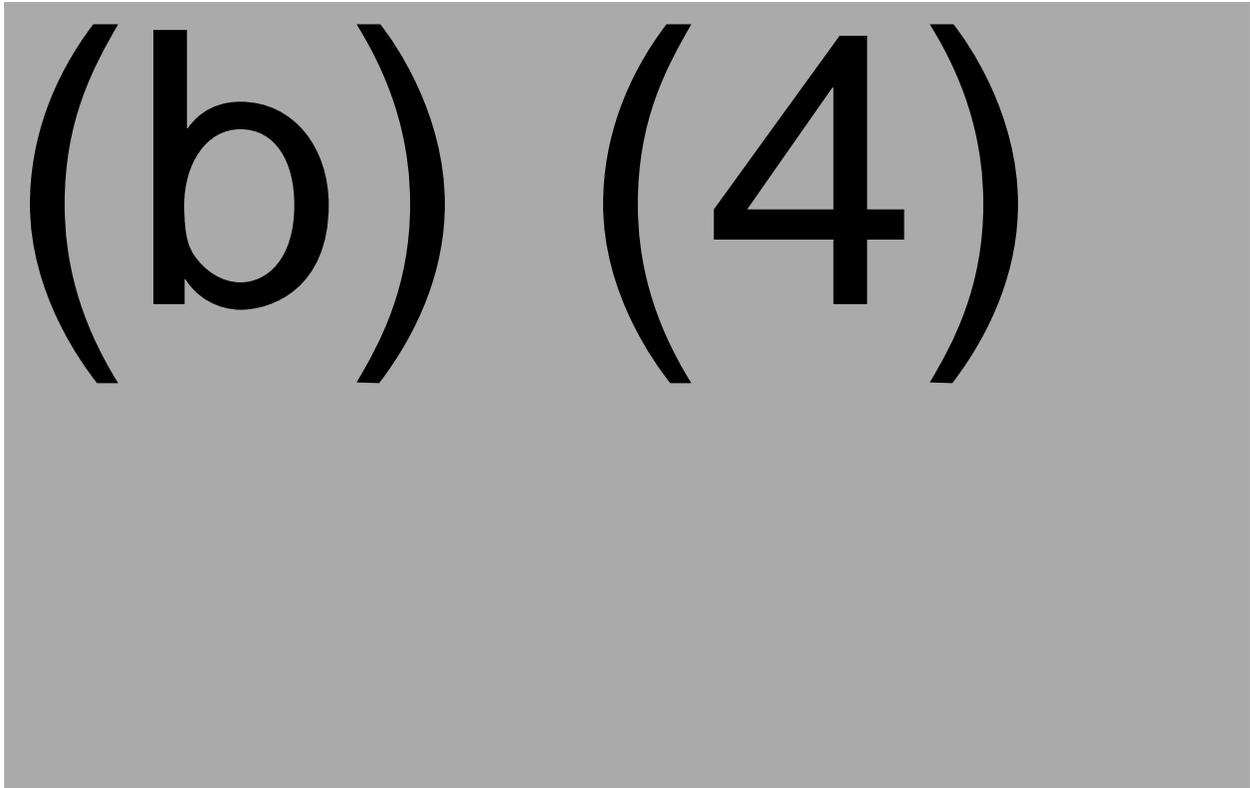
3.2.P.5.4 Batch Analyses

Reviewed by NB

The JCAR017 DP manufacturing process was modified throughout the clinical development, and product lots manufactured using (b) (4) processes were used in various clinical studies (Table 97 and Table 98). Batch analysis data is provided for product lots manufactured with pre-commercial processes versions (b) (4) and commercial process (b) (4). Results from DP lots manufactured using (b) (4) (commercial process) is depicted in the Run Charts and reviewed in section 3.2.P.5.6 Justification of Specification(s).

Table 97 Summary of JCAR017 CD4 and CD8 clinical lots manufactured at Juno Manufacturing Plant (JuMP)

(b) (4)



Reviewer comment:

1. Analysis of clinical lots manufactured using various manufacturing processes suggest that commercial manufacturing process (b) (4) results into higher success rate in manufacturing conforming lots compared to pre-commercial processes (b) (4). The success rate of above (b) (4) for (b) (4) process (the proposed commercial process) is within the range experienced for other CAR T cell products as well. Overall the batch analysis support drug product manufacturing using the commercial process (b) (4).
2. Analysis of non-conforming lots identified that failure to achieve required (b) (4) was the primary reason for non-conformance for clinical lots manufactured using the commercial process (b) (4). Sponsor has established in-process control for (b) (4). Thus, (b) (4) is assessed for each lot during manufacturing.

Lots manufactured for DLBCL cohort for study 17001:

Table 98 Summary of JCAR017 product lots manufactured at JuMP for DLBCL cohort (Study 17001)



(b) (4)

Reviewer comment: Analysis of lot disposition data submitted by the sponsor for DLBCL cohort suggest that level of non-conformance between CD4 and CD8 drug product lots is similar, and the commercial manufacturing process (b) (4) results in similar level of manufacturing success for both CD4 and CD4 DP lots.

Batch analysis for the PPQ lots contained (b) (4) leukapheresis materials manufactured using the commercial process (b) (4) and were pre-designated as PPQ batches (b) (4). The PPQ included (b) (4) - paired runs, with each paired run generating (b) (4) drug product lots. Each lot consisted of (b) (4) component for a total of (b) (4) JCAR017 lots (b) (4) DP components). A summary of the batch analyses for PPQ lots was provided, and all lots met specifications. Please see 3.2.P.3.5 Process Validation and/or Evaluation of this BLA review for PPQ lots batch analysis results.

3.2.P.5.5 Characterization of Impurities

Reviewed by NB

JCAR017 CD8 DP impurities (product and process-related impurities) are discussed in section 3.2.S.3.2 Impurities of this BLA review.

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

Data provided by Juno in these sections are acceptable and no definitive trend for deviation was identified during review of batch analysis and characterization of impurities.

3.2.P.6 Reference Standards or Materials

There is no reference standard for JCAR017. It is an autologous DP manufactured using patient's T cells. The analytical methods used to qualify DP for release use positive and negative controls and reference standards as discussed below:

(b) (4)

(b) (4)

Reviewer comment: Juno has provided detailed description of methods used to qualify standards, lot-to-lot bridging and controls, and are described in section 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures of this BLA review. Acceptable.

3.2.P.7 Container Closure System

Reviewed by KLWS

JCAR017 Primary Packaging: The (b) (4) information is cross referenced to MF (b) (4) and a consult review was provided by Laura Ricles (DCGT/CTB). Additional information pertaining to vials was provided in Amendment 24 (received on 04/01/2020), was included in the review (summarized below). Dr. Ricles concluded that the (b) (4) was acceptable for use.

The (b) (4) is a cryogenic storage container consisting of a cylindrical vial body, three ports (an injection port, a microbial barrier air vent, and a retrieval port), a retrieval port cover and associated tubing (Figure 32).

1. Loading port: The fill port is (b) (4). The fill port is a standard female Luer lock connector which is accompanied with a cap. The cap can be removed in a sterile environment and the Luer connector can be attached to a syringe for filling.
2. Air vent: Also located at the proximal end of the vial body, is a microbial-barrier air vent. The microbial barrier is a (b) (4) filter plug made of polyethylene (PE). The filter plug is (b) (4). The (b) (4) filter plug is designed to allow air to escape for easy fluid transfer without introducing contamination during filling and extraction. The (b) (4) tubing associated with the fill port and the microbial-barrier air vent are over-molded to the vial body.
3. Vial body: Cylindrical and made of commercially available (b) (4).
4. Retrieval port: Located at the distal end of the vial body, is a bottom cap with an over-molded extraction port, used for fluid extraction post-thaw. This extraction port is composed of (b) (4) and covered by an aluminum and polypropylene cover. The extraction port cover is (b) (4) onto the third closure.

(b) (4)

Sterility and Endotoxin Testing: The (b) (4) are provided sterile from (b) (4). Please refer to review by Rabia Ballica (DMPQ) for review of the sterilization validation of the (b) (4) which concluded the following: “Sterilization of (b) (4) Vial by (b) (4): Validated using appropriate ISO guidelines. No objectionable issues noted”.

Please refer to Dr. Kong’s review memo for BLA 125714 for review of the (b) (4) validation of the (b) (4). Dr. Kong concluded the following: “The (b) (4) was suitable for measuring (b) (4) on each finished of the (b) (4) product and met the specification of (b) (4).”

Shelf-life: Stability data, including various stress tests, was provided to support the proposed (b) (4) shelf-life for the (b) (4).

Extractable and Leachable: Samantha Wickramasekara (CDRH/OSEL/DBCMS) was consulted for review of the extractables and leachables information. Dr. Wickramasekara pointed out the extractables and leachables testing in MF (b) (4) was performed in 2003 and the field has evolved since then based on the scientific research and discussions. Per her suggestion the MF holder be informed to conduct updated testing according to the current guidelines. Consequently, Dr. Wickramasekara reviewed the (b) (4)-specific extractable and leachable data provided in BLA 125714 and concluded that the (b) (4) is acceptable as the DP container.

Container closure integrity testing on the DP is executed as part of the (b) (4) and is performed by the (b) (4). CCI is reviewed by Rabia Ballica, (OCBQ/DMPQ).

JCAR017 Secondary Packaging: The (b) (4) are packaged into (b) (4) holding up to four vials of each DP component (Figure 33). These two cartons are labeled and placed into an outer cryogenic storage box. The cartons are placed in a storage rack and loaded into a LN2 dewar (Figure 34) with a (b) (4)

- Commercial Packaged FDP - US Domestic.” And SOP-001481 “Commercial Final Drug Product Packaging and Labeling - US Domestic” provided in Amendment 52 (Received on 06/19/2020). Both documents include steps to maintain the COI through packaging. Adequate absorbent material able to absorb the full volume of the final drug product shipped is included inside the LN2 Shipper in the event that a leak occurs. The fully loaded LN2 Shipper is closed using (b) (4) for the entire packaging configuration.

The shipping validation study is reviewed in section 3.2.P.3.5 Process Validation and/or Evaluation of this BLA review.

Figure 33 JCAR017 Secondary Packaging

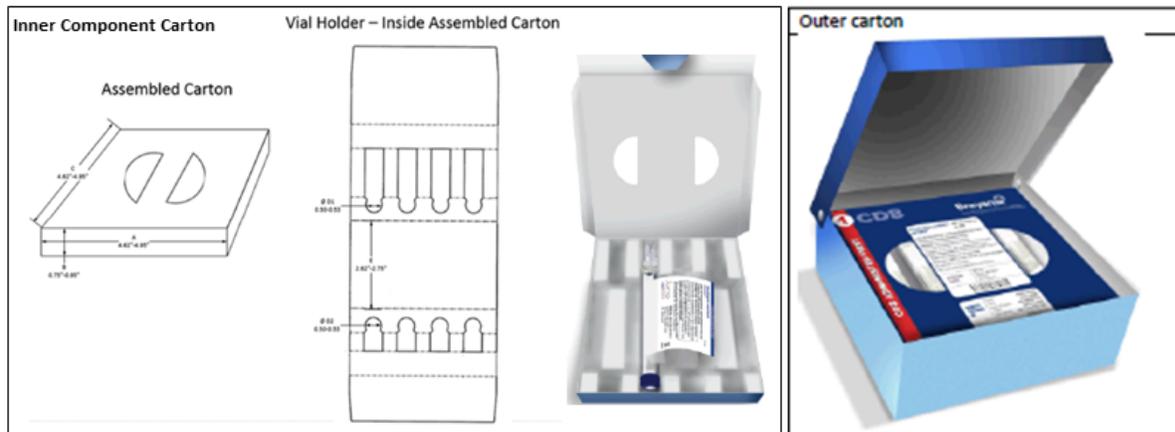


Figure 34 JCAR017 Shipping Dewar



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

The container closure and shipper information is acceptable. Adequate information was provided pertaining to the (b) (4) Vials in the BLA and in MF (b) (4). Secondary packaging is appropriate for segregation of the CD8 and CD4 DP components. No outstanding concerns were identified.

3.2.P.8 Stability

Reviewed by NB

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

JCAR017 consists of CD8 and CD4 DP components, each independently cryopreserved in (b) (4) containers at $\leq -130^{\circ}\text{C}$ in vapor phase of liquid nitrogen. The JCAR017 formulation and cryopreservation process was established to support the long-term storage of the drug product, and Juno has collected data on viability and functionality of cryopreserved DPs to assess long-term stability and in-use stability.

- 13 months shelf-life for JCAR017 CD4 and CD8 DPs was established based on results obtained from long-term stability studies.
- 2 hour in-use stability was established for JCAR017 CD8 and CD4 DPs based on in-use vial and in-use syringe stability studies.
- Temperature cycling stressed study was conducted to assess product stability at worst-case scenario and to identify stability-indicating attributes.

Long-term stability studies: Long-term stability studies were performed to support the product shelf-life for the CD8 and CD4 DPs. (b) (4) lots were used as primary batches and (b) (4) lots were used as supportive batches for long-term stability studies. All (b) (4) primary batches and (b) (4) out of (b) (4) supportive batches were cryopreserved for at least 13 months to support the proposed 13-month shelf life. The (b) (4)

(b) (4) The DP lots used in primary and supportive stability studies were manufactured using the commercial process (b) (4) at the proposed commercial manufacturing site (JuMP), and cryopreserved using the (b) (4) product. At-scale manufacturing typically produced (b) (4) containers of each DP component per batch allowing to test up to (b) (4) time points per batch. Consequently, the time points selected from multiple batches encompass a range of (b) (4) months to assess the overall product stability. Stability studies on (b) (4) primary (b) (4) and (b) (4) additional (b) (4) lots are completed. Currently, additional supportive stability studies are on-going on (b) (4) lots and (b) (4) patient lot as listed below.

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

Reviewer comment: The assessment of (b) (4) primary batches and (b) (4) supportive batches for CD4 and CD8 DP stability is completed and these batches were evaluated using specifications Juno had established during IND studies. Juno has (b) (4) additional lots (b) (4) patient) currently being evaluated for long-term stability. In Amendment 44 (received on 05/26/2020), Juno agreed to update acceptance criteria for on-going stability lots to commercial DP release acceptance criteria.

Statistical Assessment: Drug product stability over long-term storage was assessed for each parameter using Analysis of Covariance (ANCOVA) as described in ICH Q1E: Evaluation of Stability Data. For quantitative assays, statistical analysis was performed for the long-term storage condition data set to evaluate stability trends for (b) (4)

. An analysis was conducted to determine whether the lots can be (b) (4) for each stability parameter assessed in the studies. The factors selected for the ANCOVA modelling were (b) (4)

Results from long-term stability studies: All (b) (4) primary batches and (b) (4) supportive batches that met or exceeded the 13-month storage were included in statistical analysis. Stability results for each DP quality attributes are discussed below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Potency (b) (4) All batches met the protocol acceptance criteria for potency. For both CD4 and CD8 DP, all (b) (4) lots were (b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)



Additional reviewer comments for stability studies:

- 1. The analytical methods that were used to assess product stability are validated.*
 - 2. The 13-month shelf-life of DP is based on data obtained from (b) (4) lots manufactured using lentiviral vector from (b) (4) and are acceptable.*
 - 3. In IR#40 (sent on 4/23/2020), Juno was asked to provide stability data from lots manufactured using the commercial vector (b) (4) to support 13-month shelf-life. In Amendment 44 (received on 05/05/2020), Juno provided 6-month stability data available from (b) (4) PPQ stability lots (b) (4) manufactured using the (b) (4) vector that are part of on-going long-term stability studies. These PPQ lots were evaluated at time 0, 3 and 6 months. (b) (4) were measured and met lot release acceptance criteria; however, a significant change in viability and CAR+ (b) (4) was observed over time. Juno states that significance was observed due to limited number of time-points analyzed. Furthermore, they state that this trend was also observed during analysis of primary stability lots. Juno stated that updated 12-month stability data from (b) (4) PPQ lots will be submitted within 60-days before action date.*
 - 4. In amendment #65, Juno submitted up to 12-month stability data from (b) (4) PPQ lots. Analysis of stability data suggest that there is no significant change in stability indicating attributes (b) (4) of CD4 and CD8 DP over 12 months. Juno will be collecting more data up at (b) (4) months for these PPQ lots. Acceptable.*
 - 5. In amendment #71, Juno also provided 12-month stability data from (b) (4) patient lot manufactured using the (b) (4) lot data is insufficient to make a reasonable conclusion based on statistical analysis; however, all stability indicating attributes met commercial lot release acceptance criteria. Although (b) (4) showed a declining trend over time, (b) (4) were within the analytical variance of the assay. Thus, a firm conclusion cannot be made from (b) (4). Furthermore, Juno has committed evaluating (b) (4) patient lots for long-term stability. Acceptable.*
 - 6. In Amendment 44 (received on 05/05/2020), Juno also provided justification for using (b) (4) patient cells for primary stability studies. They state that (b) (4)*
- 

(b) (4)



(b) (4)



(b) (4)

In-use Stability Studies: 2 hour in-use stability was established for JCAR017 CD8 and CD4 DPs based on in-use vial and in-use syringe stability studies. The in-use stability is described in Section 3.2.P.2.2.1 Formulation Development of this BLA review.

(b) (4)



(b) (4)



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(b) (4)



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(b) (4)



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Reviewer comment: The results from temperature cycling stressed studies demonstrated that JCAR017 is not stable at those tested conditions. However, Juno concluded that there is no significant change in the stability indicating product quality attributes at stressed conditions. In Amendment 44 (received on 05/05/2020), Juno stated that this conclusion was made in an error and have revised their conclusion stating that results from stress studies demonstrate that both (b) (4) are stability indicating attributes and are significantly changed at stressed conditions. Thus, these attributes are assessed during long-term stability studies. This is acceptable.

Container Closure Assessment: The final CD4 and CD8 DP container closure integrity (CCI) was demonstrated by (b) (4) tests for durations 219

up to (b) (4) when stored at the recommended storage condition and is discussed in section 3.2.P.2.4 Container Closure of this BLA review. In addition to CCI, an additional end of shelf life sterility assessment was conducted. (b) (4) DP containers from (b) (4) patient batches manufactured at JuMP were assessed for sterility to demonstrate that container integrity is maintained over (b) (4) months at the recommended storage condition. All the tested containers passed sterility assessment supporting that the container closure system is suitable for proposed 13-month shelf life of the DP during long-term storage.

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

Juno will continue to collect DP stability data from on-going studies as described in long-term stability protocol. Juno states that stability data generated to date supports long-term storage up to 13-months at $\leq -130^{\circ}\text{C}$ in vapor phase of liquid nitrogen, and the shelf life of DP (b) (4) if additional stability data meets stability specifications. In amendment 71, Juno has committed to collect long-term stability data from (b) (4) patient lots. Furthermore, (b) (4) lot of each drug product will be placed on stability (b) (4) when a (b) (4) lot is manufactured, and long-term stability will be assessed.

Reviewer comment: The 13-month shelf-life of drug products at $\leq -130^{\circ}\text{C}$ in vapor phase of liquid nitrogen is based on stability data obtained from (b) (4) lots manufactured at JuMP using (b) (4)

Currently, Juno has (b) (4) lots that are part of on-going supportive stability studies: (b) (4) patient lot and (b) (4) lots (b) (4) and (b) (4) PPQ stability lots (b) (4). The proposed initial 13-month shelf-life is acceptable based on data from (b) (4) lots that were manufactured using the (b) (4) and stored at least 13 months. This stability data is further supported by (b) (4) PPQ lots stored for at least 12 months. Acceptable.

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

Stability data provided in the original BLA was insufficient; however, Juno provided additional information during review period as noted above. The proposed initial 13-month shelf-life for the CD4 and CD8 DPs is acceptable based on stability data from (b) (4) lots that were stored for at least 13 months.

3.2.P DRUG PRODUCT: CD4

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

Reviewed by KLWS:

JCAR017 is formulated as a single-dose cell suspension for infusion composed of autologous CD8 and CD4 DP components expressing the CD19-specific CAR. The CD4 DP is individually manufactured, formulated and cryopreserved into cryogenic vials composed of (b) (4) (4 vials per DP). Each vial contains $\geq 1.5 \times 10^6$ CAR+ viable T cells/mL.

Reviewer comment: The minimum viable T cell concentration was updated in Amendment 80 (received on 10/27/2020) in association with the communication by the FDA clinical review team for the approved dose.

3.2.P.2 Pharmaceutical Development

Reviewed by KLWS

3.2.P.2.1 Components of the Drug Product

JCAR017 is composed of equal amounts of a CD4 and CD8 CAR T cell DP component. The CD4 DP is composed of the CAR T cell (b) (4)

Table 105 JCAR017 CD4 DP composition

Constituent	Quality Standard/Grade	Function	Target Concentration (Cryopreservation vial)
CAR+ viable CD4+ T Cells	In-house	Active	≥ 1.5 x 10 ⁶ CAR+ viable T cells/mL ^a
Cryosstor® CS10 (containing (b) (4) DMSO)	In-house	(b) (4)	75% [v/v] ^b
Multiple Electrolytes Injection, Type I (b) (4)	(b) (4)	(b) (4)	(b) (4) [v/v]
Albumin (Human) Solution (25% Albumin) (b) (4)	(b) (4)	(b) (4)	(b) (4) [v/v] ^c

a Extractable volume: 4.6 mL per vial

b Final DMSO concentration in drug product is 7.5%.

c Final Albumin concentration in drug product is (b) (4).

3.2.P.2.1.1 Drug Substance

The CD4 DP is mostly composed of (b) (4). The percentage of CAR+ and CD4+ T cells varies within an allowable range for each patient lot. (b) (4) cells are the most common impurity. Compatibility of the JCAR017 with the excipients has been established during clinical development and in studies described in 3.2.P.2.2.1 Formulation Development of this BLA review.

3.2.P.2.1.2 Excipients

See review of Excipients in the CD8 DP section 3.2.P.2.1.2 Excipients.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

See review of Formulation Development in the CD8 DP section 3.2.P.2.2.1 Formulation Development

3.2.P.2.2.2 Overages

There are no overages included in JCAR017.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties of CD4 DP is same as (b) (4) and are described in Section 3.2.S.3.1 Elucidation of Structure and Other Characteristics [CD4+]

3.2.P.2.3 Manufacturing Process Development

The CD4 DP and CD8 DP manufacturing processes were developed in unison and are described together in section 3.2.P.2.3 Manufacturing Process Development

3.2.P.2.4 Container Closure System

The same container closure is used for both the CD4 and CD8 DP. See review in the CD8 DP section 3.2.P.2.4 Container Closure of this BLA review.

3.2.P.2.5 Microbiological Attributes

See review in section 3.2.P.2.5 Microbiological Attributes of this BLA review.

3.2.P.2.6 Compatibility

See review of Compatibility in section 3.2.P.2.6 Compatibility of this BLA review.

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

The CD4 DP Pharmaceutical Development is reviewed in conjunction with the CD8 DP. Acceptable.

3.2.P.3 Manufacture

Reviewed by KLWS

3.2.P.3.1 Manufacturer(s)

The Manufacturers for the CD4 and the CD8 DPs are the same. See review for CD8 DP section 3.2.P.3.1 Manufacturer(s)

3.2.P.3.2 Batch Formula

(b) (4)

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

The CD4 DP is manufactured at the JuMP facility in Bothell, WA. Each lot of the DP has a (b) (4) . Information provided is acceptable, with no deficiencies identified.

3.2.P.3.3 Description of Manufacturing Process

The CD4 and CD8 DP manufacturing processes (b) (4) :

(b) (4)

3.2.P.3.4 Controls of Critical Steps and Intermediates

See review of Controls of Critical Steps and Intermediates in the CD8 DP section

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

3.2.P.3.5 Process Validation and/or Evaluation

The CD4 DP Process Validation was conducted in concert with the CD8 DP Process Validation. The review for both DPs is in section 3.2.P.3.5 Process Validation and/or Evaluation.

Overall Reviewer's Assessment of Section 3.2.P.3.3, 3.2.P.3.4 and 3.2.P.3.5:

The CD4 DP Manufacturing process, controls, and validation are reviewed in conjunction with the CD8 DP. Acceptable.

3.2.P.4 Control of Excipients

The excipients used in the formulation of CD4 DP are the same as those being used for the CD8 DP and are described in the section 3.2.P.4 Control of Excipients of this BLA review.

Overall Reviewer's Assessment of Section 3.2.P.4: The CD4 DP excipients are reviewed in conjunction with the CD8 DP. Acceptable.

3.2.P.5 Control of Drug Product

Reviewed by NB

3.2.P.5.1 Specification(s)

Commercial specification for CD4 DP is discussed in section 3.2.P.5 Control of Drug Product of this BLA review.

3.2.P.5.6 Justification of Specification(s)

Justification of specifications for CD4 DP is described in section 3.2.P.5.6 Justification of Specification(s) of this BLA review along with CD8 DP.

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

The analytical procedures are same for CD4 and CD8 DPs and description and validation of analytical procedures are described in section 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures of this BLA review.

3.2.P.5.4 Batch Analyses

Batch analysis of CD4 DP is described along with CD8 DP in section 3.2.P.5.4 Batch Analyses of this BLA review.

3.2.P.5.5 Characterization of Impurities

Characterization of Impurities is reviewed in section 3.2.S.3.2 Impurities of this BLA review.

Overall Reviewer's Assessment of Section 3.2.P.5:

Control of the CD4 DP is reviewed in conjunction with the CD8 DP. Acceptable.

3.2.P.6 Reference Standards or Materials

There are no reference standards for the CD4 DP. Description of any additional reference standards or materials are described in section 3.2.P.6 Reference Standards or Materials of this BLA review.

3.2.P.7 Container Closure System

The container closure system is described in section 3.2.P.7 Container Closure System of this BLA review.

Overall Reviewer's Assessment of Sections 3.2.P.6 and 3.2.P.7:

The CD4 DP is reviewed in conjunction with the CD8 DP. Acceptable.

3.2.P.8 Stability

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

The CD4 DP will be stored at $\leq -130^{\circ}\text{C}$ in vapor phase of liquid nitrogen. Juno has proposed a 13-month shelf-life for the CD4 DP based on data obtained from long-term stability studies. The stability and container closure integrity of CD4 DP is discussed in the 3.2.P.8 Stability of this BLA review.

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

Post-approval stability protocol and stability commitment for the CD4 DP is discussed along with the CD8 DP in Section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment of this BLA review.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by KLWS

The facilities and equipment are described in the BLA. There are (b) (4) used for open process steps. Each (b) (4)

Refer to the DMPQ review memorandum by Rabia Ballica for full review of the facilities.

Manufacturing Capacity: Juno indicated in Amendment 60 (received 8/4/2020) that the JuMP manufacturing facility can manufacture (b) (4) JCAR017 lots, each composed of a CD8 DP and a CD4 DP, per week. Juno acknowledged that a post-licensure supplement is needed to support capacity increases.

Multiproduct Manufacturing Facility:

The JuMP facility is a multiproduct manufacturing facility that also manufactures

(b) (4)

To reduce the likelihood of cross contamination the following controls are in place:

- (b) (4)

Computerized Systems:

There are a series of validated commercial off the shelf (COTS) computerized systems used throughout the JCAR017 production:

(b) (4)

The COI and COC are maintained through SOPs that define physical and procedural controls, and electronic computer systems at each stage of the production. Figure 38 provides an overview of how different systems are integrated during the manufacturing process and summarizes relevant validated computer systems, data linkages, and process controls. Throughout the manufacturing process, COI is checked and verified (Table 106), concurrently the COC information is recorded allowing the tracking and tracing of all parties handling the product.

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.A.1:

The JuMP facility includes controls to support product segregation and COI/COC maintenance.

3.2.A.2 Adventitious Agents Safety Evaluation

Reviewed by KLWS

Because JCAR017 is composed of viable T cells, conventional sterilization and viral clearance steps cannot be incorporated into the manufacturing process. Therefore, Juno has incorporated safety at multiple steps in the manufacturing process to reduce the risk of adventitious agent contamination including:

(b) (4)

[Redacted content]

(b) (4)

[Redacted text block]

2. Environmental controls during (b) (4) JCAR017 manufacturing

- Closed processes are used when possible; all open processes are performed in a BSC
- Aseptic process simulation is conducted regularly and incorporates all process steps to verify that the process is capable of maintaining sterility
- Cleaning and decontamination of surfaces is conducted according to validated SOPs
- Environmental monitoring is performed throughout manufacturing

3. JCAR017 release testing

- Sterility
- Endotoxin
- Mycoplasma

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

Controls to reduce the likelihood of adventitious agents are in place at multiple stages in the manufacturing process. The lentiviral virus is below the limit of detection in the final DP and replication competent virus has not been detected to date.

3.2.A.3 Novel Excipients

There are no novel excipients used in (b) (4) manufacturing and formulation.

3.2.R Regional Information (USA)

Reviewed by KLWS

Executed Batch Records

Executed batch records were provided for

- (b) (4)
- JCAR017 lot (b) (4) (Both CD8 and CD4)

Unexecuted batch records were provided in amendment 22

Reviewer comment: No concerns were identified

❑ **Method Validation Package**

Summaries of detailed method validation reports were provided. Review of the analytical procedures and their validations are contained in section 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures for the (b) (4) DS and in section 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures for the JCAR017 DP.

❑ **Combination Products**

Not applicable. JCAR017 is not a combination product.

❑ **Comparability Protocols**

No formal product comparability protocols have been submitted. Manufacturing changes at the will be addressed through BLA supplements.

Other eCTD Modules

Module 1

Reviewed by KLWS:

A. Environmental Assessment or Claim of Categorical Exclusion

Juno is claiming a categorical exclusion for JCAR017 under 21 CFR 25.31 (c) from the need to prepare an environmental assessment. The applicant provided risk assessments to support the following justifications:

- (1) the application does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment;
- (2) the cells have stringent nutritional requirements for survival and replication and are not viable in the environment, and are degraded into naturally occurring substances;
- (3) T cells are terminally differentiated cells unable to proliferate or survive outside of the human body unless they are in highly controlled, tissue culture conditions;
- (4) potential for release of the lentiviral vector in the environment is considered negligible due to the low probability of free vector particle carry over in the final DP as demonstrated in the PPQ studies and discussed in Amendment 22;
- (5) the (b) (4) vector is a replication-incompetent, self-inactivated vector in which the (b) (4) and thus the likelihood of recombination to for a replication competent is extremely low and has not been detected; and
- (6) there are no known mechanisms that would enable shedding of the replication incompetent vector from JCAR017 or treated patients.

Juno has implemented risk mitigation procedures at the clinical site consistent with universal precautions for prevention of transmission of blood-borne infections. A manual is provided, and the appropriate medical personnel is trained in handling and administration of the DP and in product accountability procedures. Any unused

JCAR017 or contact materials are to be disposed of in accordance with the institution's biohazard disposal policy and local regulatory requirements for the disposal of a genetically modified product.

Reviewer comment: Juno's justifications and the rationale for claiming categorical exclusion under 21CFR 25.31 (c) from the need to prepare an environmental assessment are acceptable. The rationale supports that JCAR017 poses a negligible risk to the environment or general public. The potential for the (b) (4) vector or transduced T cells to persist is negligible. The universal precautions in place at healthcare facilities should be sufficient to mitigate the potential exposure risk.

B. Labeling Review

Reviewed by KLWS

Full Prescribing Information (PI):

Sections 2 (Dose and Administration) and 3 (Dosage Forms and Strengths)

BREYANZI is a cell suspension for infusion. A single dose of BREYANZI contains 50 to 110×10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials.

The CAR-positive viable T cell concentration varies for each lot dependent on the transduction frequency. The strength indicated on the label encompasses the entire theoretical range of possible CAR-positive viable T cells per mL. Due to the differences in transduction frequency, the volume to infuse varies between patient lots and between the CD4 and CD8 components within a single patient lot. Juno supplies a Release for Infusion (RFI) certificate with the DP to facilitate proposer dosing. Juno originally proposed that the RFI provide information to target administration of 100×10^6 CAR-positive viable T cells, the originally proposed target dose. During the review, the clinical team determined that JCAR017 was demonstrated to be efficacious between 50 to 110×10^6 CAR-positive viable T cells, and therefore the RFI should allow for dosing with in the entire range. The RFI was modified to allow the clinical site to calculate the volume per component needed to meet dose. Additionally, the RFI contains a lot-specific example to administer 110×10^6 CAR-positive viable T cells.

The PI (product insert) provides a detailed description on confirming the patient identity, preparing the required volume for each of the DP components, and sequential infusion. JCAR017 should be prepared and administered within 2 h of thaw as indicated in the PI and documented on the syringe labels.

Section 11 (Description)

BREYANZI (lisocabtagene maraleucel) is a CD19-directed genetically modified autologous T cell immunotherapy administered as a defined composition of CAR-positive viable T cells (consisting of CD8 and CD4 components). The CAR is comprised of the FMC63 monoclonal antibody-derived single-chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and

CD3 zeta activation domain. In addition, BREYANZI includes a nonfunctional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR.

BREYANZI is prepared from the patient's T cells, which are obtained from the product of a standard leukapheresis procedure. The purified CD8-positive and CD4-positive T cells are separately activated and transduced with the replication-incompetent lentiviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved as separate CD8 and CD4 component vials that together constitute a single dose of BREYANZI. The product must pass a sterility test before release for shipping as a frozen suspension in patient-specific vials.

The product is thawed prior to administration. The BREYANZI formulation contains 75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1, 1% (v/v) of 25% albumin (human).

Section 12 (Clinical Pharmacology)

The PI describes the JCAR017 mode of action; CAR binding to CD19 expressed on the cell surface of tumor and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.

Pharmacodynamic studies indicate that soluble biomarkers are detected within the first 14 days after infusion and return to baseline by 28 days. Pharmacokinetic studies indicate that infused CAR T cells exhibited an initial expansion, with maximal expansion by day 12, followed by a bi-exponential decline. CAR T cell expansion decreased as patient age increased.

Section 16 (How supplied / storage and handling)

JCAR017 is supplied with 1 to 4 vials of each of the CD4 and CD8 DP components. The number of vials per DP component supplied to the infusion site depends on the volume of each DP component required for the maximum dose. The CD4 and CD8 DP components each have a separate NDC.

The PI indicates that JCAR017 is delivered to the cell lab or clinical pharmacy associated with the infusion site. JCAR017 is shipped to the infusion site in a cryogenic dewar with a temperature monitor that has been validated to maintain $\leq -130^{\circ}\text{C}$ for (b) (4) from when it is charged with LN2. The expiration date and time is listed on the outside of the dewar. Juno indicates that infusion sites may securely maintain the product prior to administration in the shipper through the stated expiration. During qualification of the administration site, Juno may allow on-site storage if adequate facilities and controls are in place.

Reviewer comment: The DP is provided in a kit that may include 1-4 vials of each dependent on autologous lot release results. The correct dose volume is provided in an RFI Certificate that is provided with the DP. The same method of dosing was used in

clinical study 17001. The PI contains adequate instructions for thawing and dose preparation. The DP should be administered within 2 h of thaw loading the product into the syringes.

It was decided not to assign separate NDC numbers for each possible combination of CD4 and CD8 vials because the number of vials are determined after manufacture and therefore the different NDC numbers may increase confusion for the prescriber.

Carton and Container Label:

JCAR017 is supplied in an outer carton (top of carton with label shown in Figure 39) containing separate inner cartons for the CD8 and CD4 DP vials (top of carton with label shown in Figure 40). Each DP is filled in 1 to 4 single-use (b) (4) vials (Figure 41) and placed into the corresponding inner carton. Figure 33 depicts the secondary container configuration.

All labels contain the required text. Juno employed color coding on the cartons and labels to help differentiate the CD8 and CD4 DP components. The vial labels are configured in a flag design; the clear portion wraps around the vials to allow a clear view of the contents. One side of the flag contains the constant JCAR017 information and the other contains patient-specific information including lot specific information (lot number and expiration date) as well as unique patient identifiers (human-readable Name, Date of Birth, JOIN and machine-readable 2D Barcode) to confirm the patient ID prior to administration. The outer and inner carton labels contain the same information but arranged with the constant information at the top and the patient-specific information at the bottom.

Reviewer comment: *Updated product carton and vial labels, including the tradename (BREYANZI™) and non-proprietary name (lisocabtagene maraleucel) with positioning and font sizes aligning to 21 CFR 610.62 were provided in Amendment #78 (received 10/14/2020). In Amendment #81 (received 10/28/2020) Juno added the strength to each label and the NDC to the vial labels. Acceptable.*

Figure 39 Outer carton lid with label

lisocabtagene maraleucel
Breyanzi

lisocabtagene maraleucel NDC 73153-900-01
Breyanzi® Rx only

FOR AUTOLOGOUS & INTRAVENOUS USE ONLY
 Dispense with Medication Guide
Dosage: 50 to 110 x 10⁶ CAR-positive viable T cells.
 See Release for Infusion Certificate (inside shipper).
 Contains DMSO 7.5% v/v.

1 to 4 single-dose vials/component. Each vial contains 1.5 to 70 x 10⁶ CAR-positive viable T cells/mL. 4.6 mL per vial.
 Store at ≤ -130°C; vapor phase of liquid nitrogen.
 Do not filter or irradiate.
 Not evaluated for infectious substances.
 Discard unused portion.

Manufactured by:
 Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
 Bothell, WA 98021
 Phone: 1-888-805-4555 US License #: XXXXXX

 111633  NDC 73153-900-01

VERIFY PATIENT ID First: **FIRST NAME** 
 Last: **LAST NAME**
 Date of birth: **DD-MMM-YYYY**
 JOIN: **XXXX-XXXXX**
 Aph ID/DIN: **XXX XXX XXX XXX**

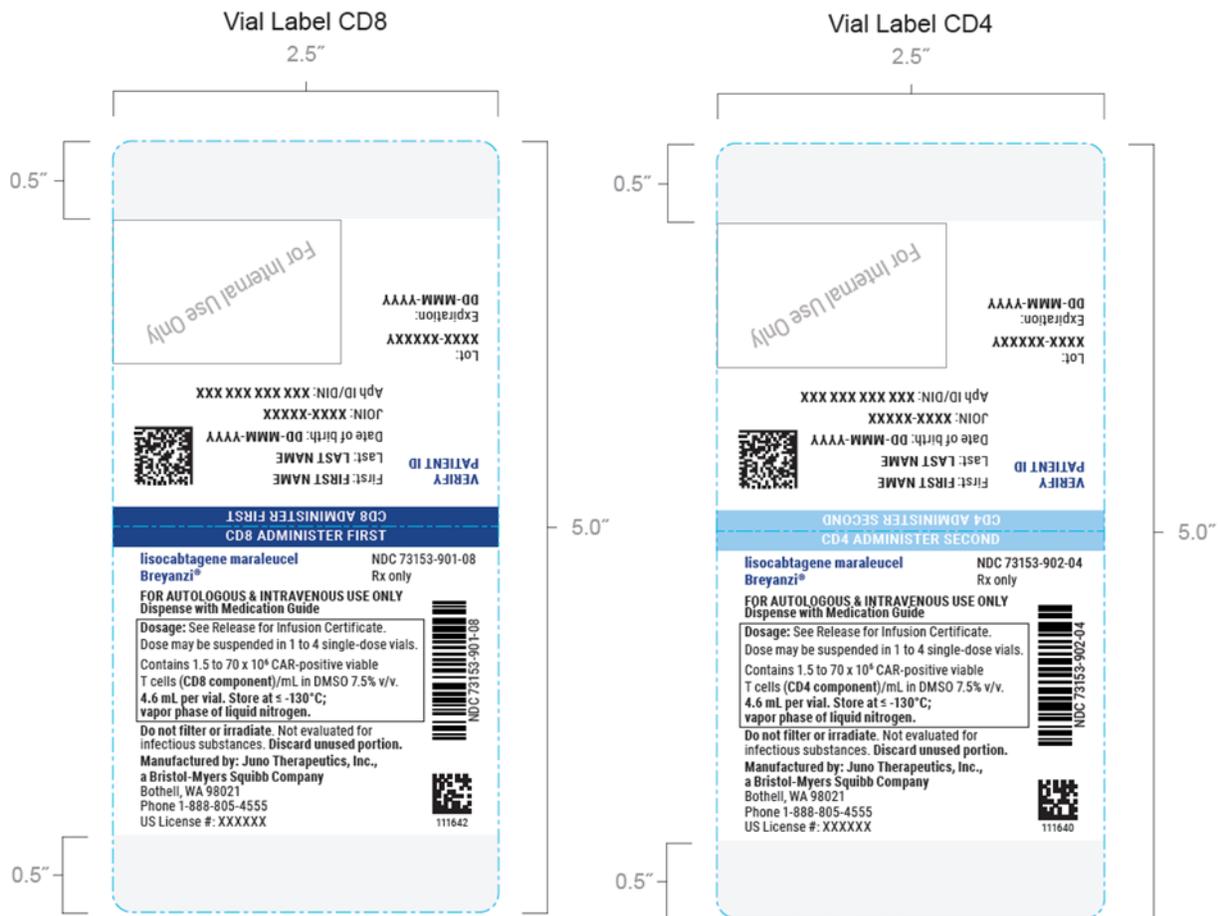
	CD8 component	CD4 component
Lot	XXXX-XXXXXY	XXXX-XXXXXY
Expiration	DD-MMM-YYYY	DD-MMM-YYYY

STOP **Confirm patient ID prior to infusion**

Figure 40 Inner carton lids with labels



Figure 41 Vial labels



Modules 4 and 5

Reviewed by NB

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

Pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and RCL were assessed using validated, qualified, or exploratory methods (Table 107). The JCAR017 PK was determined using (b) (4)

[Redacted]

. The PD effects of JCAR017 were assessed by (b) (4)

[Redacted] . RCL was assessed using (b) (4)

(b) (4)

(b) (4)

(b) (4)

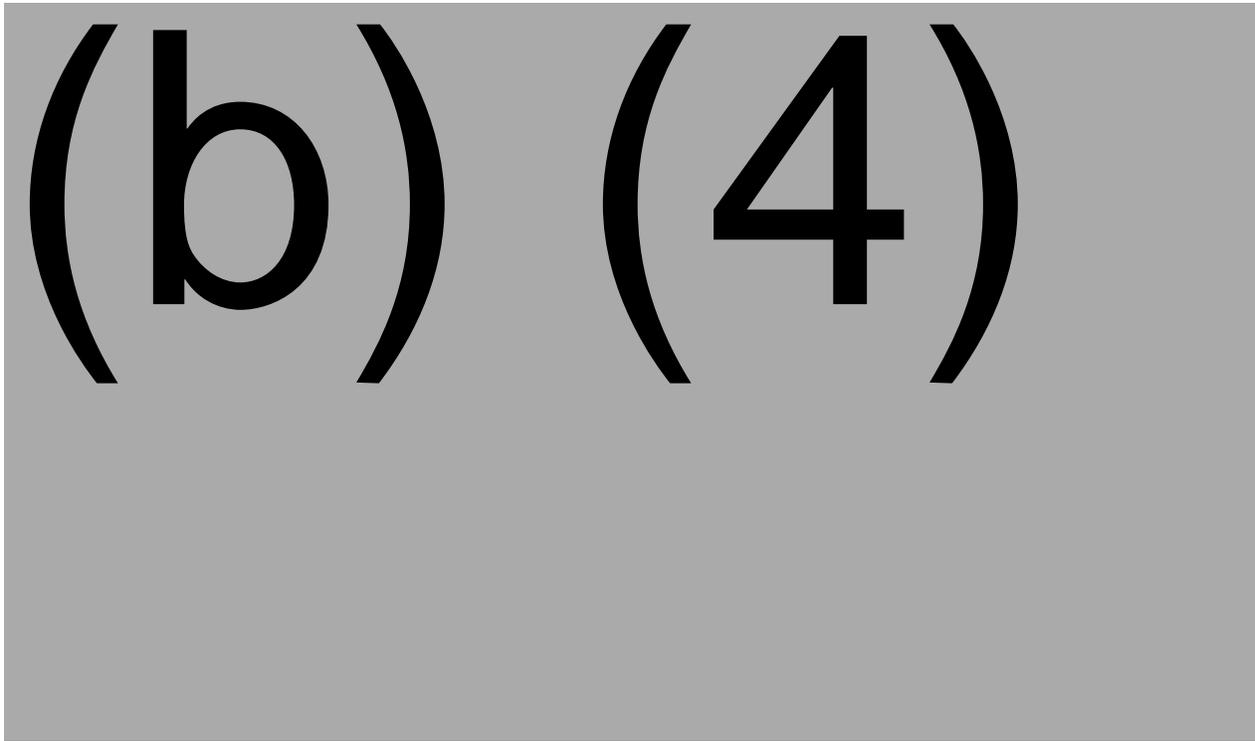
1 page determined to be not releasable: (b)(4)

Reviewer comment: The assay is specific, reproducible, and met the pre-specified acceptance criteria. Assay is adequately validated and deemed fit-for-purpose. Acceptable.

(b) (4)



(b) (4)



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

(b) (4)

Reviewer comment: The assay has been validated by (b) (4) for Fit-for-Purpose (FFP). Juno is performing this assay for exploratory endpoints and has not validated in their context of use. This is acceptable.

(b) (4)

Reviewer comment: This is a qualified assay, which has been used in study 17001 without any issue. The assay qualification study assesses key assay parameters which is adequate for this assay to be used for its intended purpose. Acceptable.

Due to absence of suitable animal model, for JCAR017 standard single/repeated dose toxicity, PK and biodistribution studies were deemed not meaningful and were not conducted. Similarly, in vivo nonclinical safety pharmacology, toxicokinetic, genotoxicity, carcinogenicity, developmental safety, or reproduction toxicity studies were not conducted.

Overall Reviewer’s Assessment of Relevant Sections of Module 4 and 5: Assay methods used in clinical PK/PD and immunogenicity assessment are adequately described and either validated or qualified and fit for purpose. SOPs for bioanalytical methods were provided in Amendment 58 (received on 07/21/2020), and validation/qualification reports were provided in the BLA. Acceptable.