

BLA STN#125643/0

Proper (non-proprietary) name:
Axicabtagene ciloleucel

Proprietary name:
Yescarta™

Manufacturer:
Kite Pharma, Inc.

Reviewers:
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DCGT CMC Review Data Sheet

1. **BLA#:** STN 125643
2. **REVIEW DATE:** November 29, 2017
3. **PRIMARY REVIEW TEAM:**
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RPM: Mark Davidson
4. **MAJOR GRMP DEADLINES:**
Filing Meeting: 5/30/17
Mid-Cycle Meeting: 7/14/17
Late-Cycle Meeting: 9/11/17
Primary Review Due: 7/28/17
Secondary Review Due: 8/30/17
PDUFA Action Date: 11/29/17
5. **COMMUNICATIONS WITH SPONSOR AND OTAT:**

Communication/Document	Date
BLA Acknowledgement	April 25, 2017
BLA Filing Notification	May 25, 2017
Midcycle teleconference communication	July 21, 2017
REMS Notification Letter	August 1, 2017
Late Cycle Meeting	September 11, 2017

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
Amendment #11 (COC/COI Validation)	4/28/17	Yes
Amendment #15 (CMC IR sent 5/5/17)	5/11/17	Yes
Amendment #17 (CMC IR sent 5/12/17)	5/18/17	Yes
Amendment #22 (CMC IR sent 5/19/17)	5/26/17	Yes
Amendment #25 (CMC IR sent 5/26/17)	6/1/17	Yes
Amendment #29 (CMC IR sent 6/5/17)	6/12/17	Yes
Amendment #34 (CMC IR sent 6/19/17)	6/29/17	Yes
Amendment #44 (CMC IR sent 7/19/17)	7/27/17	Yes

5/26/17, and 6/19/17)		
Amendment #46 (Response to Mid-Cycle Meeting)	8/4/17	Yes
Amendment #54 (CMC IR sent 8/16/17)	8/18/17	Yes
Amendment #59 (CMC IR sent 8/28/17)	8/28/17	Yes
Amendment #60 Stability Update	9/11/17	Yes
Amendment #70 (CMC IR sent 9/26/17)	9/28/17	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: YESCARTA™
- b. Trade Name: YESCARTA™
- c. Non-Proprietary/USAN: axicabtagene ciloleucel
- d. UNII: U2I8T43Y7R

8. PHARMACOLOGICAL CATEGORY: CD19-directed genetically modified autologous T cell immunotherapy

9. DOSAGE FORM: Cell suspension

10. STRENGTH/POTENCY: 2×10^6 viable CAR T cells/kg

11. ROUTE OF ADMINISTRATION: Intravenous infusion

12. REFERENCED MASTER FILES:

(b) (4)

13. INSPECTIONAL ACTIVITIES: Pre-Licensing Inspection completed 6/22/17

14. CONSULTS REQUESTED BY DCGT:

BB-MF (b) (4)

The consult review was completed 7/19/17 by Nailong Zhang, PhD, Product Quality Reviewer, CDER/OPQ/OBP/DBRR IV, and concluded that the information provided in BB-MF (b) (4) is adequate to support the BLA.

15. PRECEDENTS: None

16. ADMINISTRATIVE

Signature Block

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OTAT, CBER	
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SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation:

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product axicabtagene ciloleucel. The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics. This information, satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

II. List Of Deficiencies To Be Communicated:

All CMC related deficiencies identified during the BLA review have been fully addressed by Kite Pharma, Inc. There are no outstanding CMC deficiencies.

III. List Of Post-Marketing Commitments/Requirement:

Major safety risks have been identified that require a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). The risks include Cytokine Release Syndrome (CRS) and neurological toxicities in the acute phase after treatment. A REMS notification letter was sent to Kite Pharma on 8/1/17. In addition, delayed safety risks have been identified that may include secondary malignancy. Details regarding Kite Pharma's proposed patient registry were requested in an 8/14/17 information request (IR) and submitted 8/18/17. The patient registry follows 1500 patients treated with axicabtagene ciloleucel for long term delayed adverse effects (including secondary malignancy) for 15 years (see OBE Review for details).

IV. Review Of Common Technical Document - Quality Module 1

The information provided in Module 1 of the CTD includes a cover letter and Forms FDA 1571, 356h and 3674; administrative information; Letters of Authorization; correspondence regarding BLA related meetings; Pediatric administrative information (including a request for waiver from pediatric studies); information amendments not covered under modules 2-5; other correspondence (including a section on environmental analysis); labeling, risk management plan; and proprietary name.


A. Environmental Assessment or Claim of Categorical Exclusion

The requested action qualifies for and complies with categorical exclusion under 21 CFR 25.31c as described in the FDA Guidance for Industry Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral and Microbial Products. Therefore, an environmental assessment was not prepared. The product consists of human cells that are unable to survive or proliferate in the environment outside of the human body. The potential for release of the retroviral vector in the environment is also considered negligible due to the low probability of viral particles present in the final drug product and the design of the virus to be replication incompetent.

V. Primary Container Labeling Review:

Two labels are included in each final product infusion bag, the product bag label and patient identification. Example labels are provided below. See APLB review for additional comments on acceptability of product labels.

Reviewer Comment: *Sample labels provided in the original submission were not compliant with 21 CFR 610.62. The position and font of the proper name were not as prominent as the trade name. Sample labels also did not include a Kite Pharma phone number. The sponsor was asked to provide revised labels (CMC IR dated 8/28/17 and 9/26/17). The sponsor provided revised labels included below in Amendment #70.*



NDC 71287-119-02

axicabtagene ciloleucel
YESCARTA™

Rx ONLY FOR AUTOLOGOUS & INTRAVENOUS USE ONLY
No U.S. standard of potency

Dose: One sterile bag for infusion.
Contents: Maximum of 2 x 10⁸ autologous anti-CD19 CAR T cells in approximately 68 mL suspension containing 5% DMSO USP.

Gently mix the contents of the bag while thawing

See package insert for full prescribing information and instructions for administration

Ship and store in vapor phase of liquid nitrogen ≤ -150°C

DO NOT FILTER
DO NOT IRRADIATE

Manufactured with gentamicin


Not evaluated for infectious substances

Preservative free

Manufacturer: Kite Pharma, Inc., El Segundo, CA 90245
Phone: 1-844-454-KITE U.S. Lic. #XXXX

AS-00732

VERIFY PATIENT ID **axicabtagene ciloleucel**
YESCARTA™

Lot: 123456789-0X 

Kite Patient ID: 123456789


Expiration Date: 31-Dec-2900


First Name M.I.: FIRST NAME W

Last Name: LAST NAME

DOB: 31-Dec-1900

Hospital Patient ID: 1234567890123456

DIN: 

AS-00731 W0123 45 678900 

VI. Review Of Common Technical Document-Quality Module 3

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT**3.2.S DRUG SUBSTANCE** (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.2.P DRUG PRODUCT

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

Axicabtagene ciloleucel consists of autologous T cells that have been genetically modified *ex vivo* to express a chimeric antigen receptor (CAR) to target CD19 on the cell surface of malignant B cells. The active substance of axicabtagene ciloleucel is composed of a patient's cells that has undergone *ex vivo* T cell activation, gene transfer by replication-deficient retroviral vector (b) (4) [REDACTED] Vector), and expansion. These transduced T cells are then formulated in a cryopreservation medium suitable for infusion. Each final product bag of axicabtagene ciloleucel is filled to deliver a target dose of 2.0×10^6 CAR T cells/kg of patient weight. Axicabtagene ciloleucel is supplied cryopreserved at a temperature of $\leq -150^\circ\text{C}$ in cryostorage bags. The cryostorage bag contains a nominal 68 mL of axicabtagene ciloleucel. Table 55 lists the components of axicabtagene ciloleucel.

Table 55. Components of Axicabtagene Ciloleucel

Component	Amount per Bag (nominal 68 mL)	Function	Reference to Quality Standard
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Anti-CD19 CAR T-cells	(b) (4) CAR T-cells/kg to a maximum allowable dose of 2×10^8 CAR T-cells	Active Ingredient	N/A
(b) (4)	(b) (4)	(b) (4)	BB MF (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Albumin (human), (b) (4)	(b) (4)	(b) (4)	(b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The active component of axicabtagene ciloleucel comprises CD3-positive T cells that have been transduced with an anti-CD19 CAR retroviral vector. See Section 3.2.S.3.2 for information on cellular components and impurities. The T cell subset composition varies from subject lot to subject lot. The product may also contain a small percentage of autologous natural killer (NK) cells or cells with a phenotypic characteristic of NK T cells. These cells generally comprise less than (b) (4) of axicabtagene ciloleucel. B cells, monocytes and other white blood cells are not present at detectable levels (3.2.S.3.2 Impurities). The characteristics of axicabtagene ciloleucel lots manufactured as part of the ZUMA-1 Phase 2 campaign are listed in Table 56.

Table 56. Characteristics of Axicabtagene Ciloleucel from ZUMA1 Phase-2 Subject Lots

Characteristic	Median and Range	Number of Lots Analyzed
(b) (4)	(b) (4)	(b) (4)
Total Cells per Dose	2.4×10^8 (b) (4)	(b) (4)

Excipients used in the manufacture of axicabtagene ciloleucel include Albumin (human) (b) (4) See 3.2.P.4 Control of Excipients for additional information on excipients.

3.2.P.2.2 Drug Product

3.2.P.2.2.2 Overages

Axicabtagene ciloleucel is formulated at the target dose of 2×10^6 T-cell/kg patient body weight. Overages are included in the drug product formulation and fill. However (b) (4) bags of infusion product are made in each manufacturing run [for more details see 3.2.S.2 Manufacture (Kite Pharma, Inc, axicabtagene ciloleucel)].

3.2.P.2.2.3 Physicochemical and biological properties

The biological properties of axicabtagene ciloleucel are described in 3.2.S.3.1 Elucidation of Structure and Other Characteristics. The chemical properties of the formulation are described in 3.2.P.2.1 Components of the Drug Product. The final formulation is frozen and stored in a vapor phase liquid nitrogen freezer with demonstrated stability up to 9 months in the final container product (3.2.P.8 Stability). Thawed product is administered at room temperature with demonstrated stability up to 3 hours (3.2.P.2.6 Compatibility). The biological properties of axicabtagene ciloleucel are not impacted by the formulation. This data confirms that the physical structure of the cell, biochemical structure of the expressed Anti-CD19 CAR and biological response of the product are maintained.

3.2.P.2.3 Manufacturing Process Development

Formulation

The final product formulation is described in 3.2.P.1 Description and Composition of the Drug Product. A series of developmental studies were conducted to determine the optimal formulation for axicabtagene ciloleucel cryopreservation. These experiments assessed (b) (4)

(b) (4)

Reviewer Comment: The information provided is acceptable. These studies support the current formulation.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Cryopreservation in (b) (4)

Following the Formulation step, the final product bag(s) is transferred to a cassette (b) (4) or equivalent) for cryopreservation in a (b) (4) freezer (b) (4) using a defined program. The program consists of a (b) (4)

A series of developmental studies were conducted to determine the optimal conditions for axicabtagene ciloleucel cryopreservation. These experiments assessed the point at which the product formulation (b) (4)

Reviewer Comment: *The information provided is acceptable. These studies support the current (b) (4) freezing program.*

3.2.P.2.4 Container Closure System

The primary container closure is a 510(k)-cleared (b) (4) cryostorage bag (b) (4) intended for storage of blood and blood products (this is fully described in Section 3.2.P.7). The same bag, along with a smaller version of manufactured from the same material by the same supplier, was used during clinical development of the product, including long term and accelerated stability studies. Extractables and leachables studies (reviewed in Section 3.2.S.2.6.10), and container closure integrity testing (reviewed under Section 3.2.P.7) were performed, demonstrating suitability of these bags.

3.2.P.2.5 Microbiological Attributes

The capacity of the primary container closure system (b) (4) bags) to provide a barrier against ingress of microbial contaminants has been qualified by container closure integrity testing using a (b) (4)-based method. This testing is reviewed under Section 3.2.P.7.

3.2.P.2.6 Compatibility

The thawed final drug product is to be administered by infusion using standard venous access catheter and non-filtered tubing. Compatibility studies with FDA cleared devices for venous access were not performed. Axicabtagene ciloleucel is derived from apheresis material and therefore is compatible with devices cleared for transfusion of blood products.

To support up to a 3 hour hold time after thaw, three studies were performed to assess in-use stability. All studies involved comparison of samples taken immediate post thaw to those held at room temperature for up to 3 hours. The first 2 studies were each performed on 3 lots of axicabtagene ciloleucel manufactured from donor apheresis material and filled into the (b) (4) bags. Results for all tests (including (b) (4) anti-CD19 CAR expression, potency by (b) (4), T-cell (b) (4) cell count, viability, and recovery) were comparable between freshly thawed samples and samples held at room temperature for 3 hours.

The third study was performed on 3 lots of axicabtagene ciloleucel manufactured at (b) (4) and filled into the full-size (b) (4) bags. Additional time points at 0.5, 1, 1.5, and 2 hours were added in this study to provide more detailed information on the temporal aspects of the axicabtagene ciloleucel in-use stability profile. For each of the 3 lots, results for all tests (b) (4), potency (b) (4) and cell count, viability, and recovery] were comparable among samples tested immediately after thaw (time zero) and samples held at room temperature at all time points up to 3 hours. Potency by (b) (4) and viable cell counts are shown in Figure 18 and Figure 19. Line in these figures represents the acceptance criteria.

Figure 18. Potency by (b) (4) of axicabtagene ciloleucel held at room temperature

(b) (4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer

The manufacturer of axicabtagene ciloleucel is Kite Pharma, Inc. (b) (4), 2355 Utah Avenue El Segundo, CA 90245, USA (FEI: 3012583739, DUNS: 963353359)

3.2.P.3.2 Batch Formula

A list of all components in the axicabtagene ciloleucel dosage form, their amounts on a per batch basis, and a reference to their quality standards is provided in Table 55.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The axicabtagene ciloleucel manufacturing process proceeds (b) (4) to formulation. For the purposes of this section on manufacturing process and process controls, DP

manufacture includes final formulation in cryopreservation media, inspection and labeling product, cryopreservation, and storage and transport of the final product (Figure 20).

Figure 20. Flow Diagram of the Downstream Axicabtagene Ciloleucel Manufacturing

(b) (4)

The formulation process is described in more detail below.

(b) (4)

(b) (4)

Final Formulation

Based on the total number of viable CAR+ T cells manufactured and the calculated final container dose, (b) (4)

Inspection, Freezing, Storage and Shipment

The final product on (b) (4) for final product inspection. The appearance test is conducted as described in 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s). The final product cassettes are then transferred to a (b) (4) freezer using predefined freezing program. After completion of this program the final product is transferred (b) (4) for long term storage. The final product is shipped to qualified clinical sites in a pre-charged liquid nitrogen dewar as described in 3.2.P.7 Container Closure System.

3.2.P.3.4 Controls of Critical Steps and Intermediates

As described in 3.2.P.3.3 Description of Manufacturing Process and Process Controls the formulation does not have critical control steps and does not involve intermediates. Kite Pharma has performed a process failure mode and effects analysis to identify risks associated with formulation and has conducted studies to mitigate these risks. These characterization studies support a range of formulation components and final product mix times as summarized in Table 58. In addition, Kite Pharma has performed studies to support up to (b) (4) as a worst case sample) of the final formulated product prior to freezing in (b) (4) (see 3.2.P.2.3 Manufacturing Process Development)

Table 58. Formulation Process Parameter Characterization

Process Parameter	Characterized Range	Normal Operating Setpoint	Parameter Classification (Critical/Non-critical)
(b) (4)	(b) (4)	(b) (4)	Non-critical
			Non-critical
			Non-critical
			Non-critical
			Non-critical

3.2.P.3.5 Process Validation and/or Evaluation

Process validation was performed for (b) (4) manufacturing at (b) (4) and for the chain of custody/chain of identity (COC/COI). These are reviewed as separate studies below. The (b) (4) manufacturing process validation study also included a (b) (4) in the event of a software failure.

Process Validation

(b) (4)

(b) (4)

The systems used to initiate, control and trace chain of identity are described below:

Kite Konnect (KK) is a web-based, customer relationship management system that initiates chain of identity with assignment of the Kite Patient ID number and records patient-identifying information.

Enterprise Business System (EBS) is a suite of business applications used for manufacturing, supply chain, financial and quality business process flow transactions. EBS assigns cell order and COI/lot number, generates and prints label with COC numbers in barcode and human readable formats, records manufacturing COC events and generated COC reports.

(b) (4) is a web application for apheresis material that records apheresis information (including patient identity) and interfaces with courier tracking systems to record and track shipment status. (b) (4) also generates a final COC event for receipt of final product at treatment site

(b) (4) is label printing software that receives XML files from EBS to format and print labels.

Two PPQ studies were conducted to assess suitability of COI and COC at (b) (4) following written procedures that specified a minimum of (b) (4) confirmatory manufacturing runs executed using the integrated systems, manufacturing batch records and SOPs for commercial product. Each study specified a minimum of (b) (4) manufacturing runs initiated with fresh donor material and at least (b) (4) using (b) (4).

For the first study, VAP-0004, (b) (4) lots were manufactured using apheresis for (b) (4) healthy donors. (b) (4) of the lots manufactured met the acceptance COC and COI criteria per protocol except for Final Product Bag (b) (4). During the EBS transaction for packout of Lot (b) (4), a break in COC was observed. An investigation was performed to identify the root cause of the break in the COC. The investigation revealed that the root cause was that the EBS system was not configured to detect inadvertent selection of an incorrect lot from a different cell order with a different COI. EBS system and procedural corrective actions were implemented to restrict the available lots to the corresponding COI.

A subsequent validation protocol (VAP-0006) using (b) (4) additional final product shipments was executed to validate that the changes implemented in EBS after VAP-0004 were effective. Documentation collected in VAP-0006 included the following:

- a) Lot Traveler report (from EBS).
- b) Courier system generated waybills.
- c) Executed copies of the sample chain of custody forms.
- d) In-Process, (b) (4) PBMC Bag, Final Product Bag, Final Product Cassette and
- e) LN2 Shipper Labels.
- f) Manufacturing and packout, Chain of Custody Reports from EBS
- g) Final COC report from (b) (4)

Acceptance criteria included the following:

(b) (4)

All (b) (4) additional final product shipments in VAP-0006 met the COI and COC acceptance criteria with no exceptional conditions.

Reviewer Comment: COI/COC PPQ is acceptable. The integrated systems used to create, control and trace COI and COC for axicabtagene ciloleucel commercial manufacturing processes is considered validated.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

Excipients used in the manufacture of axicabtagene ciloleucel are listed in Table 64. Each lot of excipient is received, inspected, sampled, tested, and dispositioned in accordance with written procedures.

Table 64. Excipients Used in the Manufacture of axicabtagene ciloleucel

Reagent	Current Vendors/Suppliers	Grade
Albumin (Human) (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

The specification for (b) (4) is provided in Table 65. (b) (4) is a defined cryopreservation medium, formulated with (b) (4), in which all components are GMP-grade, are purchased from approved suppliers and are compendial materials when available.

Table 65. Specifications for (b) (4)

(b) (4)

(b) (4)

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

Albumin (Human) (b) (4) test methods comply with relevant sections of (b) (4) and 21 CFR 640.80-84.

Information regarding the analytical procedures and the validation of these for (b) (4) is provided in (b) (4) Drug Master File (BB-MF (b) (4)). The identity test method utilized by Kite Pharma for receipt of each lot of (b) (4) method consistent with (b) (4).

3.2.P.4.4 Justification of Specifications

Justification for (b) (4) specification is provided in (b) (4) Drug Master File (BB-MF (b) (4)). This includes testing for critical quality attributes that are relevant to use in axicabtagene ciloleucel, including: (b) (4)

3.2.P.4.5 Excipients of Human or Animal Origin Human Serum Albumin (b) (4), sourced from (b) (4), is manufactured per GMP regulations, complies with both (b) (4), as well as 21 CFR 640.80-84 and is FDA approved for intravenous use. This product is a derivative of human plasma collected exclusively from US donors in accordance with all applicable regulations for the manufacture of human biological products. All lots of albumin include certifications that: 1) all donations of plasma were individually tested and found non-reactive to HBV sAg, HIV-1/HIV-2 Ab, and HCV Ab; and 2) each plasma pool was tested and found negative for HBsAg, HIV-1/HIV-2 Ab, and HCV RNA (by (b) (4)). All lots are also tested for sterility and endotoxin.

There are no components of human origin in (b) (4), and the only component of animal origin is (b) (4). As described in BB-MF (b) (4), the supplier has provided the relevant certifications to assure that the (b) (4) is free of agents associated with TSE/BSE.

3.2.P.4.6 Novel Excipient

None

3.2.P.5 Control of Drug Product

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

Axicabtagene ciloleucel specifications are presented in Table 66. The timing of sample acquisition for each lot release test is depicted in Figure 23. Justification for each specification and the timing of sampling is provided in the narrative below.

Table 66. Specifications for Axicabtagene Ciloleucel

Test	Method	Method Number	Acceptance Criteria
Appearance	Visual inspection	SOP-0317-QC3	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles.
Identity	(b) (4) for the scFv heavy chain variable region, linker and CD28 sequences	TM-0009-QC3	(b) (4)
Dose ¹	Viable cell count/Anti-CD19 CAR expression	TM-0005-QC3 TM-0001-QC3	(b) (4) anti-CD19 CAR T cells/kg (maximum allowable dose: 2×10^8 anti-CD19 CAR T cells)
Potency	Cell viability	TM-0005-QC3	(b) (4)
	Anti-CD19 CAR expression	TM-0001-QC3	(b) (4)
	(b) (4)	TM-0002-QC3	(b) (4)
Purity	(b) (4)	TM-0010-QC3	(b) (4)
	Gentamicin	TM-0033-QC3	(b) (4)
	Endotoxin	TM-0004-QC3	(b) (4)
Microbiological tests	Mycoplasma (b) (4) method	TM-0006-QC3	(b) (4)
	Sterility	TM-0007-QC3	No growth
Testing for Retrovirus	RCR by (b) (4)	TM-0008-QC3	(b) (4)
	RCR (b) (4)	(b) (4)	Negative ²
(b) (4)	(b) (4)	(b) (4)	(b) (4)

¹ Dose is prepared based on patient weight, viable cell concentration and (b) (4).

² Product is released based on results from RCR by (b) (4). Result from RCR by (b) (4) is provided with final lot closure.

Figure 23. Timing of Sampling for Axicabtagene ciloleucel Lot Release Testing

(b) (4)

Appearance

This specification was established based upon observation of clinical axicabtagene ciloleucel lots in the final container closure. Appearance testing is the final test performed on the final formulated product prior to (b) (4)

Identity

This specification was established based on the specificity (b) (4) the scFv heavy chain variable region, linker and CD28 sequences of the (b) (4) gene, the transgene sequence that encodes the anti-CD19 CAR protein.

Dose

Axicabtagene ciloleucel is manufactured to a target dose of 2.0×10^6 viable anti-CD19 CAR T cells per kg patient weight. The acceptance criterion of (b) (4) viable anti-CD19 CAR T cells per kg (maximum allowable dose: 2×10^8 anti-CD19 CAR T cells) was established based on the dose range defined in the ZUMA-1 clinical protocol. The number of anti-CD19 CAR T cells is determined using the viable cell count (b) (4) and the (b) (4) of anti-CD19 CAR-positive T cells determined b (b) (4)

Cell viability

This specification was based on the cell viability data from axicabtagene ciloleucel ZUMA-1 clinical lots which ranged from (b) (4). Based on this data, the lower specification limit for cell viability was established at (b) (4). Axicabtagene ciloleucel lots manufactured from donor apheresis material in the PPQ campaign at (b) (4) ranged from (b) (4). A sample is taken to assess cell viability following (b) (4), to have the data available so axicabtagene ciloleucel can be formulated appropriately. Data from stability studies (SBL-0011, SBL-0020), have demonstrated that cell viability test results, taken from the final product container, are comparable to cell viability results taken from the (b) (4) material.

CD19 CAR expression (b) (4)

This specification was based on the results from (b) (4) axicabtagene ciloleucel clinical lots which were used to estimate lower and upper specification limits using a 2-sided tolerance interval with 95% proportion coverage at the 95% confidence level. This (b) (4) lots contained Phase 1 & 2 axicabtagene ciloleucel lots plus (b) (4) additional clinical lots manufactured after the completion of the ZUMA-1 study, during the period from (b) (4), for use in the third cohort of the ZUMA-1(14) and the ZUMA-6 (3) clinical trials. The (b) (4) of the axicabtagene ciloleucel clinical lots ranged from (b) (4), with a mean of (b) (4); the statistically-determined lower and upper acceptance limits were calculated as (b) (4) respectively (Table 67, Figure 24). These calculated limits were rounded to (b) (4) for the specification. All axicabtagene ciloleucel lots manufactured from donor apheresis material in the PPQ campaign at (b) (4) yielded results within the acceptance limits, ranging from (b) (4) with a mean of (b) (4). The sample used to assess (b) (4) is taken following the (b) (4) step has no mechanistic impact on the results of this assay and the data are required prior to formulation so axicabtagene ciloleucel can be formulated appropriately.

(b) (4)

(b) (4)

(b) (4)

Gentamicin

This specification was established based upon demonstrated process capability and patient-monitoring history. Data from (b) (4) axicabtagene ciloleucel process characterization lots demonstrated a worst-case amount of gentamicin per product dose of (b) (4). Data from the (b) (4) axicabtagene ciloleucel PPQ lots manufactured at (b) (4) yielded a similar calculated worst-case gentamicin content of (b) (4) per dose. Based on the current demonstrated process capability, the specification limit has been set at (b) (4) gentamicin per axicabtagene ciloleucel dose. Kite

Pharma stated that this limit was set with a margin of safety until additional manufacturing experience is obtained and process capability is further characterized. To put it in context of a normal patient dose, this specification also represents less than (b) (4) IV loading dose of gentamicin for a 45-kg patient. In addition to the gentamicin specification limit, (b) (4)

Endotoxin

This specification was established to ensure that a patient weighing 45 kg or above, receiving a 68-mL infusion of axicabtagene ciloleucel over 30 minutes, will be exposed to endotoxin levels below the (b) (4) threshold described in (b) (4). The sample is taken for endotoxin testing (b) (4)

Mycoplasma

The specification of (b) (4) was established in accordance with regulatory and safety requirements. The sample for mycoplasma testing is taken (b) (4) step. A limited number of aseptic manipulations occur (b) (4), and processing times are short, therefore the risk of mycoplasma introduction (b) (4) is low.

Sterility

The specification of 'no growth' was established in accordance with regulatory and safety requirements. The sample is taken for sterility testing (b) (4)

RCR (b) (4)

The specification of 'negative' was established in accordance with regulatory and safety requirements. Sample for RCR testing is taken (b) (4)

RCR (b) (4)

The specification of (b) (4) was established in accordance with regulatory and safety requirements. Sample for RCR testing is taken (b) (4) step, (b) (4)

(b) (4)

Retention samples

Kite Pharma, Inc. has requested an exception from complying with the full requirements for final product retention samples as stated in 21 CFR 600.13 due to the size of the batches of axicabtagene ciloleucel produced and the desire to use all the available material. Kite Pharma is proposing a tiered approach to its final product retention sample plan. Additional information on this approach was requested from Kite Pharma and was provided in Amendment 22. All retention samples will be kept for at least (b) (4) after the patient dose is administered. After the (b) (4) retention time, Kite Pharma may discard the samples per documented internal procedures.

- Tier 1

- (b) (4)

- Tier 2

- (b) (4)

- Tier 3

- (b) (4)

- Second patient dose

- (b) (4)


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

Final product release testing is conducted at (b) (4). Some analytical methods were originally validated at Kite Pharma's clinical manufacturing site (b) (4) and were

subsequently transferred to its commercial manufacturing site (b) (4). For these tests an abbreviated transfer validation was performed (repeatability, intermediate precision and reproducibility). The decision to only assess precision was based on the following conditions: equipment and software make and model are identical between the sites, materials and supplies are identical between the sites, (b) (4) analysts were trained at (b) (4) and the methods being used are identical between the sites.


Appearance

Visual inspection of the container closure system and its contents for color, clarity and particulate matter is conducted per SOP-0317-QC3, and is performed by trained personnel using (b) (4)



Identity

Identity of axicabtagene ciloleucel is confirmed, when performing (b) (4) testing (TM-0009-QC3), (b) (4)



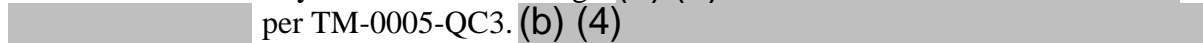
Detection of (b) (4), above the limit of quantitation, was demonstrated to be specific for the (b) (4) gene. Please see description of (b) (4) testing for additional information.

Dose

Axicabtagene ciloleucel is dosed based on the number of viable anti-CD19 CAR-positive T cells per kilogram (kg). Dose is determined using the viable cell count (TM-0005-QC3) and the percentage of anti-CD19 CAR-positive T cells as determined by (b) (4) (TM-0001-QC3). Axicabtagene ciloleucel is manufactured to a target dose of 2.0×10^8 anti-CD19 CAR T cells per kg patient weight. The acceptance criterion of (b) (4) anti-CD19 CAR T cells per kg (maximum allowable dose: 2×10^8 anti-CD19 CAR T cells) was established based on the dose range defined in the ZUMA-1 clinical trial. The patient entire dose is filled into one bag in an approximate volume of 68 mL

Cell count & viability

Cell count and viability are determined using a (b) (4) per TM-0005-QC3. (b) (4)



(b) (4)

Reviewer Comment: (b) (4) were used to evaluate repeatability and intermediate precision; therefore, no data was provided on the repeatability/intermediate precision of the assay with regard to determining cell viability upon transfer to (b) (4). However, data was provided for the reproducibility of the assay with regard to determining viability so this is acceptable.

Anti-CD19 CAR expression (b) (4)
Anti-CD19 CAR expression on the surface of the autologous T cells that make up axicabtagene ciloleucel is measured using a (b) (4) assay per TM-0001-QC3. This assay utilizes a (b) (4)

Reviewer Comment: (b) (4). Kite Pharma provided a revised SOP in Amendment 34 that included guidelines for setting each (b) (4) during compensation and acquisition of the (b) (4) controls. This is acceptable.

Validation of the anti-CD19 CAR expression (b) (4) assay was originally conducted at (b) (4) (QR-0259) and was subsequently transferred to (b) (4) (QR-0579). Summaries of the validation data and transfer validation data are presented in Table 71 and Table 72.

Reviewer Comment: (b) (4) validation was not provided in the original submission. This information was requested and was provided in Amendments 34 and 44 and has been incorporated into the tables below.

Instrument performance at (b) (4) was demonstrated through successful (b) (4) Setup and Tracking (b) (4) set-up and successful acquisition of compensation (b) (4) during the compensation set-up (QP-0579). Inter-instrument comparability between the main and backup instruments at (b) (4) was assessed during assessment of intermediate precision and between the main instruments at (b) (4) during assessment or reproducibility.

(b) (4)

Gentamicin

Gentamicin content of axicabtagene ciloleucel is measured using a commercially available (b) (4) per TM-0033-QC3. (b) (4)

Reviewer Comment: The gentamicin (b) (4) was validated using the (b) (4) (b) (4), however, the comparability between the (b) (4) (b) (4) was shown during the validation of the (b) (4) (b) (4) utilize the same software (b) (4) to operate, acquire, and analyze the data; (b) (4) utilize the same method templates for the acquisition of data; (b) (4) The demonstration of (b) (4) comparability and gentamicin (b) (4) validation were both acceptable.

Validation of the gentamicin (b) (4) was conducted at (b) (4); the validation data is summarized in Table 77.

Table 77. Method Validation Summary for the Gentamicin (b) (4)

(b) (4)

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

(b) (4)




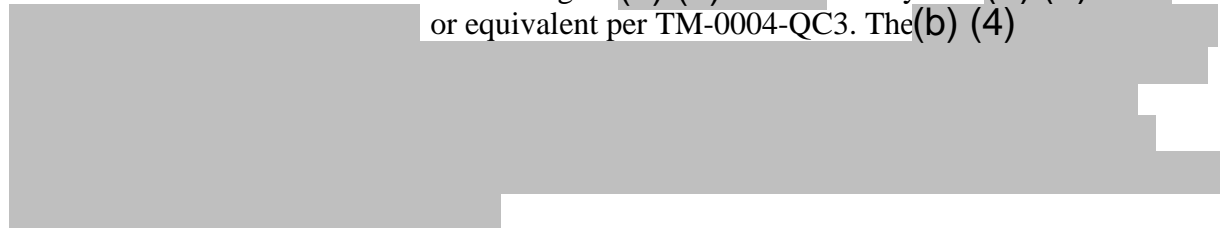
Table 79. Method Transfer Validation Summary for Determination of (b) (4) by (b) (4)

(b) (4)



Endotoxin

Endotoxin contamination is measured using the (b) (4) test system (b) (4) or equivalent per TM-0004-QC3. The (b) (4)



Reviewer Comment: Review of the validation of this method (QR-1116) was conducted by DBSQC. The validation was found to be acceptable. See DBSQC review for more details.

Mycoplasma


To test for mycoplasma, axicabtagene ciloleucel is (b) (4)



Reviewer Comment: Review of the validation of this method (QR-0500, QR-0775) was conducted by DBSQC. The validation was found to be acceptable. See DBSQC review for more details.

Sterility


The sterility of axicabtagene ciloleucel is measured using the (b) (4) per TM-0007-QC3. This method uses (b) (4)



Reviewer Comment: Review of the validation of this method (QR-0437) and its transfer to (b) (4) (QR-0731, QR-1106, QR-1181) was conducted by DBSQC. The validation was found to be acceptable. See DBSQC review for more details.

RCR (b) (4)

(b) (4) is used to detect and quantify the (b) (4) as an indicator of the presence of RCR in axicabtagene ciloleucel for lot release per TM-0008-QC3. This assay includes (b) (4)



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

(b) (4)

RCR (b) (4)
The RCR (b) (4) assay is used to confirm RCR (b) (4) results and is conducted per SOP# (b) (4)
Axicabtagene ciloleucel is (b) (4)

Validation of the (b) (4) RCR assay was described under 3.2.S.4.3 Validation of Analytical Procedures.

***Reviewer Comment:** Kite Pharma has provided sufficient analysis and data to demonstrate that the analytical methods used for axicabtagene ciloleucel manufacturing are suitable for their intended use.*

3.2.P.5.4 Batch Analyses

(b) (4) axicabtagene ciloleucel process performance qualification (PPQ) lots have been manufactured from healthy donor apheresis material at (b) (4)

(b) (4). A summary of the batch analyses was provided and all lots met specifications. Please see Table 62 (3.2.P.3.5 Process Validation and/or Evaluation) for a summary of results.

3.2.P.5.5 Characterization of Impurities

The overall bioburden control strategy encompasses manufacturing process design features and procedural controls that have been implemented to minimize the potential for introduction and proliferation of microbial contaminants. These include using single use, sterile consumables and filtering (b) (4). The ability to remove process-related impurities has been characterized during process development leaving only 2 impurities, (b) (4) and gentamicin, to be measured as part of lot release. A description of the (b) (4) and gentamicin specifications and their justification are present in 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s). A description of the (b) (4) and gentamicin analytical assays and their validation are present in 3.2.P.3.5 Process Validation and/or Evaluation.

3.2.P.6 Reference Standards or Materials

An axicabtagene ciloleucel positive control test material (PCTM) is used as an assay control for the (b) (4) release assays. The full-scale development lots (b) (4) have been used as positive control test material to support analytical method development and validation, method transfer and clinical quality control testing. The same formulation, cell concentrations (b) (4) and freezing procedure as axicabtagene ciloleucel was utilized, however, (b) (4) per an approved SOP. Cells were evaluated for (b) (4) (b) (4). Results from Lot (b) (4) were also trended over (b) (4) months and were similar to initial mean values.

New manufactured lots of PCTM will be prepared using full scale manufacturing production records. Subsequently, (b) (4)

(b) (4) per approved SOP. The lot must meet axicabtagene ciloleucel lot release criteria.


Additionally, to establish the range for a new positive control test material, a minimum of (b) (4) vials will be tested as independent samples for (b) (4) production. The upper and lower control limits for (b) (4) used to determine assay validity, will be calculated by mean values (b) (4) standard deviations. The current stability data supports a (b) (4) month PCTM shelf-life.

***Reviewer Comment:** Other than the PCTM, no other reference material was described in the submission; additional information on reference standards used for the following assays was requested and was supplied in Amendment 22.*

Cell Viability

- (b) (4)

(b) (4)

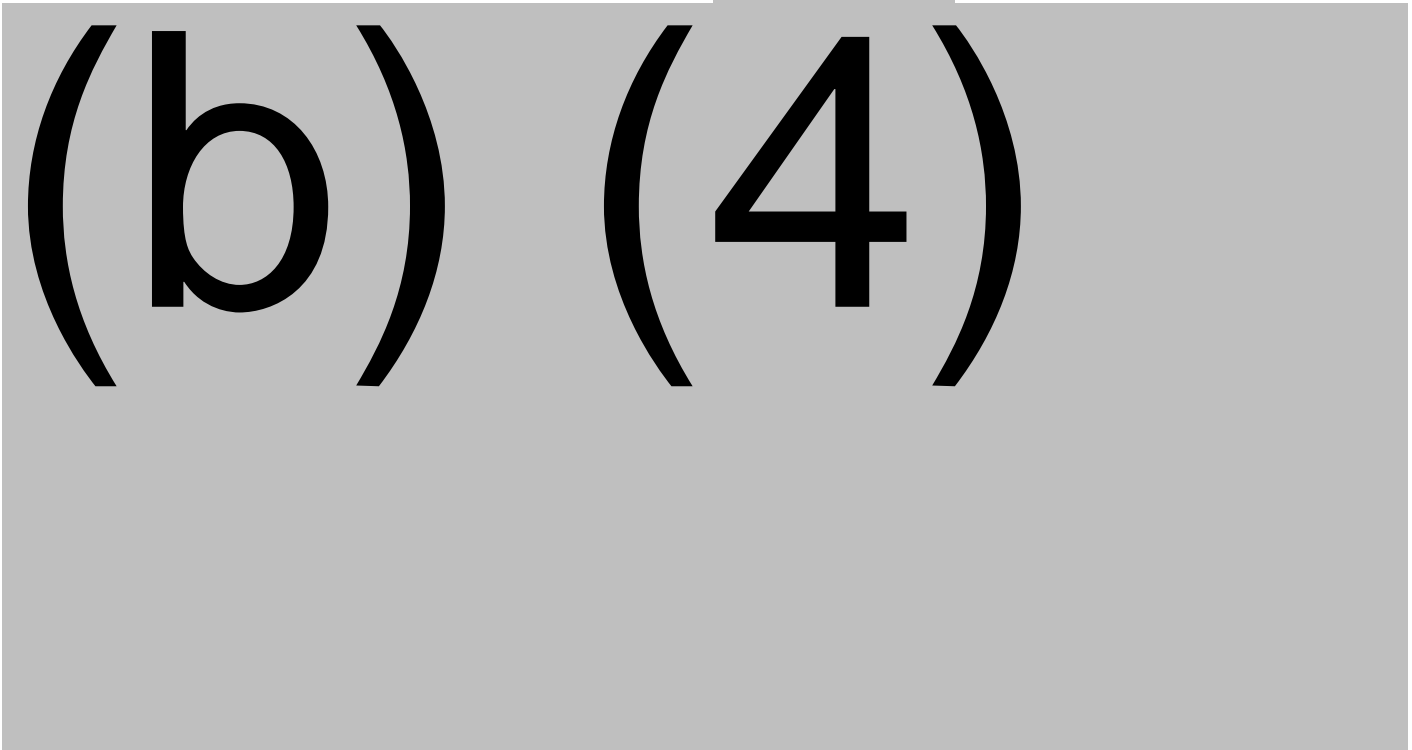


3.2.P.7 Container Closure System

The primary container closure system for axicabtagene ciloleucel DP is an (b) (4) cryostorage bag (b) (4) manufactured by (b) (4) (Figure 26 and Table 81). This bag is an FDA 510(k) cleared Class II medical device intended for use as an empty container for collection and processing of blood and blood components. Note that these (b) (4) bags are also used for (b) (4)

Figure 26. Final Product Container Closure (b) (4)

(b) (4)



(b) (4)

The bag is aseptically filled via the attached tubing set. Once filling is complete, the tubing is (b) (4). Kite Pharma's specification for the bag is provided in (Table 82) and a vendor CoA is provided and acceptable.


Table 82. Kite Pharma specification for (b) (4) crvobag

(b) (4)

Reviewer Comment: Note that the (b) (4) bag has a maximum freeze volume of (b) (4) with an intended freeze volume of (b) (4). Copies of the Kite Pharma materials master specification (document MS-00129) for the (b) (4) bag, including details of acceptance criteria and testing, were provided in amendment 18 (response to CMC IR of 11MAY2017). This information is acceptable.

(b) (4) bags are the primary container closure for axicabtagene ciloleucel (see 3.2.P.7 Container Closure System). (b) (4) (see Section 3.2.S.6 Container Closure System (b) (4) however (b) (4) bags were used as a surrogate because they are constructed from the same material as (b) (4). Extractables studies using (b) (4) bags with and without labels, and with (b) (4) bags with labels as follows (Table 83):

(b) (4)



Container closure integrity

Closure integrity was assessed using a (b) (4) test method (described in Section 3.2.P.2.5.) for both (b) (4) storage bags (the latter used for stability studies). In the (b) (4) test, (b) (4)

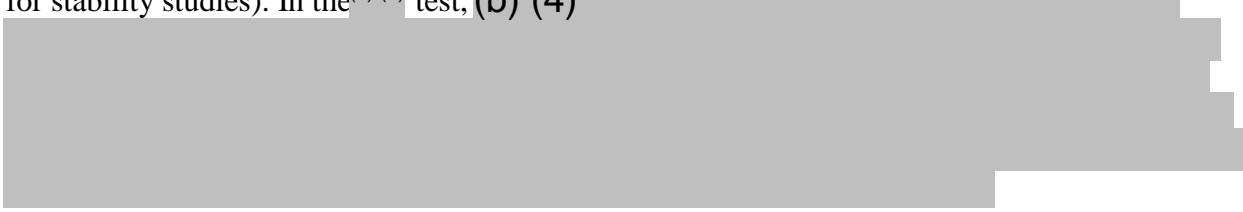



Table 84. (b) (4) test qualification results

(b) (4)



All test bags (without holes) passed the previously defined acceptance criteria, whereas all positive controls with (b) (4) failed, demonstrating test system suitability.

(b) (4)



s

(b) (4)

(b) (4)

Reviewer Comment: The test bags passed the acceptance criteria by a large margin. While acceptance criteria were previously determined using (b) (4) bags rather than positive control bags filled with mock product, this difference should not matter as testing is performed using bags (b) (4). Note that observed (b) (4) for filled bags (Table 85) were similar to those seen for (b) (4) bags (Table 84). The (b) (4) test method should be regarded as qualified (not validated per (b) (4) to detect manufacturing and closure defects down to (b) (4). However, as the (b) (4) bags are already 510(k) cleared for storage of blood products, this level of testing is acceptable.

Secondary Packaging (Aluminum (b) (4))

Once filled and sealed, each (b) (4) cryobag is placed into an aluminum cassette (Table 86) to provide protection during storage, shipment, and handling. Schematic diagrams of this cassette are provided and acceptable.

Table 86. Secondary Packaging (aluminum (b) (4))

Component	Description	Supplier	510(k) Clearance
(b) (4)	Aluminum cassette (b) (4)	(b) (4)	N/A

Reviewer Comment: The aluminum (b) (4) is intended only to protect the product bags and will not directly contact the product at any time. There is sufficient clearance in each dimension to accommodate filled (b) (4) bags. The proposed secondary packaging is therefore acceptable.

Vapor Phase Liquid Nitrogen Shipper

Axicabtagene ciloleucel (contained in (b) (4) bags with aluminum (b) (4)) is shipped to treatment sites in a vapor phase liquid-nitrogen (LN₂) shipping container (Table 87).

Table 87. Vapor phase LN₂ shipper

Component	Description	Supplier	510(k) Clearance
-----------	-------------	----------	------------------

Component	Description	Supplier	510(k) Clearance
(b) (4)	Vapor phase liquid nitrogen shipper	(b) (4)	N/A

The shipper is comprised of a protective plastic outer container with an internal cushion and a lid with pressure release valves. The dry shipper dewar and vapor plug lid are loaded into this outer container, and secured with an absorbent fabric ring that fits around the dewar neck. The shipper (b) (4) by Kite Pharma Materials Management prior to loading by (b) (4)

(b) (4) value is checked to be $\leq -150^{\circ}\text{C}$ and recorded.

The frozen product cryobag contained in an aluminum cassette is removed (b) (4). The product cryobag is inspected, and the cassette is placed into a (b) (4). The bagged cassette is then packed into the dewar surrounded by 6 (b) (4) absorbent socks (cylindrical polymer bags containing shredded (b) (4), manufactured (b) (4). The time of loading is recorded, the shipper vapor plug replaced, and the absorbent ring placed around the vapor plug. The vapor plug is secured with a blue zip tie bearing a unique serial number (as a tamper indicator), and documentation (CoA, shipper certificate, copy of requisition, return waybill, and empty sticker) is placed in the inside lid pouch. The shipper is then closed, latched, and sealed with white zip ties. Waybills and “Exempt Human Specimen” and “Do Not X-Ray” stickers are attached to the outside of the shipper. The shipper is then transferred to the courier agent.

***Reviewer Comment:** Information concerning shipper preparation and loading was provided in Amendment 18 (response to CMC IR of 12MAY2017), along with a detailed SOP (SOP-0389-MM3). The shipping container and procedures are acceptable.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The stability of axicabtagene ciloleucel under long term ($\leq -150^{\circ}\text{C}$) storage conditions is under investigation. Stability testing under accelerated (b) (4) stress (b) (4) and in-use (post-thaw) conditions is complete.

3.2.P.8.1.1. Summary of long-term stability studies

A total of (b) (4) lots of axicabtagene ciloleucel have been assessed for stability under long term ($\leq -150^{\circ}\text{C}$) storage conditions. (b) (4) lots manufactured at the (b) (4) commercial facility and (b) (4) engineering lots manufactured at the (b) (4) facility are in ongoing long term stability studies, and an additional (b) (4) lots manufactured at the (b) (4) facilities have completed long-term stability studies (Table 88).

Reviewer Comment: Comparability between lots produced using the (b) (4) process at (b) (4) has been demonstrated (see Section 3.2.S.2.6), making lots produced at (b) (4) suitable for use in stability studies. No data is provided in the BLA submission regarding comparability of lots produced at (b) (4). However, no stability conclusions are drawn solely from studies on (b) (4) lots alone. This is acceptable.

Table 88. Axicabtagene ciloleucel long-term stability lots (stored at $\leq -150^{\circ}\text{C}$)

Lot number	Date of manufacture	Manufacturing site	Study duration	Most recent time point tested	Complete/Ongoing
(b) (4)	(b) (4)	(b) (4)	3 months	3 months	Complete
			3 months	3 months	Complete
			3 months	3 months	Complete
			12 months	12 months	Complete
			12 months	12 months	Complete
			12 months	12 months	Complete
			12 months	12 months	Complete
			12 months	12 months	Complete
			12 months	12 months	Complete
			(b) (4)	6 months	Ongoing
			(b) (4)	6 months	Ongoing
			(b) (4)	6 months	Ongoing
			6 months	6 months	Complete
			6 months	6 months	Complete
			6 months	6 months	Complete
			6 months	6 months	Complete
			(b) (4)	6 months	Ongoing
			(b) (4)	6 months	Ongoing
			(b) (4)	6 months	Ongoing
Manufactured from (b) (4) PBMC (other lots manufactured using (b) (4) material)					

Long-term stability data from clinical lots manufactured at (b) (4) and stored at $\leq -150^{\circ}\text{C}$ are available for up to 12 months. All samples met the commercial acceptance criteria for product and container appearance at each time point (summarized in Table 89), with additional tests for (b) (4) was also assessed in some early studies.

Reviewer Comment: Note that certain analytical methods were replaced with improved methods for some studies (e.g., (b) (4) for viability, and CD19-CAR detection reagents changed from (b) (4). Note also that while limited stability studies were performed on patient and donor derived product in the primary container closure used for commercial product ((b) (4) bags), many stability studies used samples stored in the (b) (4) bags. Stability testing using the same container closure as that for commercial distribution is required per cGMP regulations [21 CFR 611.166(4)]. However, use of (b) (4) bags allows (b) (4). The (b) (4) bags are manufactured by the same supplier, from the same material and have been tested and found similar to the (b) (4) bags in terms of closure integrity (Table 84 and Table 85) and product cryopreservation attributes. Use of the (b) (4) bags for stability studies is therefore acceptable.

Table 89. Axicabtagene ciloleucel stability test methods

Stability Test ¹	Test method	Protocol acceptance criteria	Commercial acceptance criteria ²
Appearance	Visual	(b) (4)	(4)
(b) (4)	(b) (4)		
(b) (4)	(b) (4)		
Cell viability			
Anti-CD19 CAR expression			
Potency			
(b) (4)			
Sterility			

¹ Not all tests performed in all stability studies

² Commercial acceptance criteria for comparison only; Individual stability studies used various acceptance criteria

³ Not included in commercial specification

⁴ Method used in early studies but replaced with different method in later studies

Reviewer Comment: The justification for use of stability protocol acceptance criteria that differed from the commercial acceptance criteria was requested in CMC IR dated 26 May 2017 and explained in amendment 26. Stability protocol acceptance criteria were based on the release criteria at the time of stability study initiation, whereas commercial acceptance criteria are based on statistical analyses of available patient data for (b) (4) production. All stability data are compared with commercial release criteria. A description of the stability protocol acceptance criteria at each stage of product development is provided in Amendment 26. This justification is reasonable. For review purposes, the commercial acceptance criteria are used to draw conclusions on product stability, regardless of the protocol acceptance criteria.

For the clinical lots manufactured at (b) (4) and stored at ≤ -150 °C for up to 12 months, (b) (4) were relatively constant at each time point tested (ranging from (b) (4) respectively). Viability results met the commercial criteria (b) (4) at all time points, as did (b) (4) potency results (range (b) (4) 1). Anti-CD19 CAR expression criteria were met in all cases, except for (b) (4) at 1 month which was slightly above the upper limit of (b) (4) (result (b) (4) method: not significantly different from the time 0 value of (b) (4) were measured in early stability studies and similar relative patterns of (b) (4) were seen over time. All samples remained sterile at all time points.

For lots manufactured at (b) (4), data have been collected only through 6 months (studies are ongoing). All commercial acceptance criteria have been met, except for 2 exceptions in Anti-CD19 CAR expression (lot (b) (4) had values of (b) (4) at 3 and 6 months, respectively: these values exceeded the commercial acceptance criteria, but were within the

stability protocol acceptance criteria of (b) (4)

Graphical summaries for viability (Figure 27), anti-CD19 CAR expression (Figure 28), and potency by (b) (4) (Figure 29) are shown for lots used in long term stability studies (studies that only went out to 3 months are not shown in the graphs for clarity).

Figure 27. Viability of axicabtagene ciloleucel after long-term storage at $\leq -150^{\circ}\text{C}$



LR: lot release (testing done only on (b) (4) lots prior to (b) (4)); Dashed line represents the commercial acceptance criterion. Data shown are from the (b) (4) method.

Reviewer Comment: A slight dip in viability was seen at 3 months in the (b) (4) lots, but not the (b) (4) lots. However, there is no apparent overall change in viability based on the data provided. This is acceptable.

Figure 28. Anti-CD19 CAR expression (b) (4) of axicabtagene ciloleucel after long-term storage at $\leq -150^{\circ}\text{C}$



LR: lot release (testing done only on (b) (4) lots prior to (b) (4)); Dashed lines represent commercial acceptance criteria. Data shown are from the CD19 (b) (4) method.

Reviewer Comment: In the (b) (4) lots no decrease in CAR expression is seen out to 3 months, although there is a trend for slightly increased CAR expression at 1 month relative to time 0. CAR expression subsequently decreases (on average (b) (4) of time 0 at 6 months [95% CI (b) (4) $n=(b) (4)$, and (b) (4) of time 0 at 12 months [95% CI (b) (4) $n=(b) (4)$ although the commercial acceptance criterion of (b) (4) CAR expressing cells is exceeded at all times. This trend is not seen for the (b) (4) lots, although data is available only to 6 months.

Figure 29. Potency (b) (4) of axicabtagene ciloleucel after long-term storage at $\leq -150^{\circ}\text{C}$



LR: lot release (testing done only on (b) (4) lots prior to cryopreservation); Dashed lines represent commercial acceptance criteria.

Reviewer Comment: In the (b) (4) lots there was decreased (b) (4) relative to lot release at the time 0 point (62% of the lot release value [95% CI (b) (4) $n=(b) (4)$), but then a general trend towards higher (b) (4) at subsequent times (for example, at 6 months an average 231% increase relative to lot release [95% CI (b) (4) $n=(b) (4)$). This trend is mirrored in the (b) (4) lots (except that there is no initial drop, likely due to the lack of (b) (4) [lot release] testing on these lots), with an apparent plateau reached after 3 months (at 3 months (b) (4) of T=0 value [95% CI (b) (4) $n=(b) (4)$; at 6 months (b) (4) of T=0 [95% CI (b) (4) $n=(b) (4)$, and at 12 months (b) (4) of T=0 [95% CI (b) (4) $n=(b) (4)$. Despite these trends for increased (b) (4), a 2 to 3-fold increase for the stability lots would remain within the commercial acceptance range of (b) (4).

Stability studies were performed on (b) (4) lots manufactured from patients for clinical trial use but not administered. These lots were filled into the commercial container closure (b) (4) bags) and stored in vapor phase liquid nitrogen ($\leq -150^{\circ}\text{C}$). Data are shown in Table 90.

Table 90. Axicabtagene ciloleucel patient lot stability testing

Test method	(b) (4)		(b) (4)		(b) (4)		(b) (4)	
	Lot release	4.5 months	Lot release	6 months	Lot release	12 months	Lot release	(b) (4) months
Appearance	NS ⁵	NS	NS	Pass	NS	Pass	NS	Pass

Test method	(b) (4)		(b) (4)		(b) (4)		(b) (4)	
	Lot release	4.5 months	Lot release	6 months	Lot release	12 months	Lot release	(b) (4) months
(b) (4)	(b) (4)							
Cell count								
(b) (4)								
Cell count								
(b) (4)								
Anti-CD19 CAR								
(b) (4)								
Anti-CD19 CAR								
(b) (4)								
Potency by (b) (4)								
(b) (4)								
Sterility	No growth	No growth	No growth	NT	No growth	No growth	No growth	No growth

¹ Lot (b) (4) manufactured (b) (4)

² Lot (b) (4) manufactured at (b) (4)

³ Lot (b) (4) manufactured at (b) (4)

⁴ Lot (b) (4) manufactured (b) (4)

⁵ Not scheduled

⁶ Not tested

Reviewer Comment: While all commercial and protocol acceptance criteria were met after storage at $\leq -150^{\circ}\text{C}$ for several months in all product lots tested, there was a (b) (4) drop in (b) (4) (compared to lot release values) after thawing (except for lot (b) (4) which had (b) (4) of initial activity after thawing at (b) (4)). It is unclear whether this is a one-time drop (reflecting post-freeze/thaw changes) after which (b) (4) would remain similar at later time points, or if the decrease in (b) (4) is part of a downward trend. In addition, there was an apparent shift in (b) (4) for lot (b) (4) where the proportions of (b) (4) after storage more than doubled compared to values seen at lot release, with concomitant decreases in proportions of (b) (4) cells. As the relative contributions of different T cell populations is unclear, the significance of this cannot be assessed. (b) (4). No major changes in viability or % CD19 CAR expression were seen in these patient lots out to (b) (4). Note that none of these lots were manufactured at (b) (4). Additional patient lots should continue to be studied for stability (see Section 3.2.P.8.2. Post-approval stability protocol).

3.2.P.8.1.2 Summary of accelerated stability studies

Accelerated stability studies at (b) (4) were performed on (b) (4) clinical lots manufactured at (b) (4) and (b) (4), as shown in Table 91.

Table 91. Axicabtagene ciloleucel accelerated stability lots (stored at (b) (4))

(b) (4)

(b) (4)

3.2.P.8.1.3 Summary of stress stability studies

Stress stability studies at (b) (4) for up to (b) (4) were performed in 2 studies on a total of (b) (4) clinical trial lots (Table 92). These studies were designed to assess the ability of various tests to indicate product stability.

Table 92. Axicabtagene ciloleucel accelerated stability lots (stored at (b) (4))

Lot Number	Date of Manufacture	Manufacturing Site
(b) (4)		

The stress stability studies are outlined in Table 93.

Table 93. Axicabtagene ciloleucel stress stability (b) (4) studies

(b) (4)

¹ NS: not scheduled

² Using (b) (4) method, as noted in Amendment 26 (response to CMC IR of 26MAY2017)

(b) (4)


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Figure 30. Axicabtagene ciloleucel viability under stress stability (b) (4) conditions

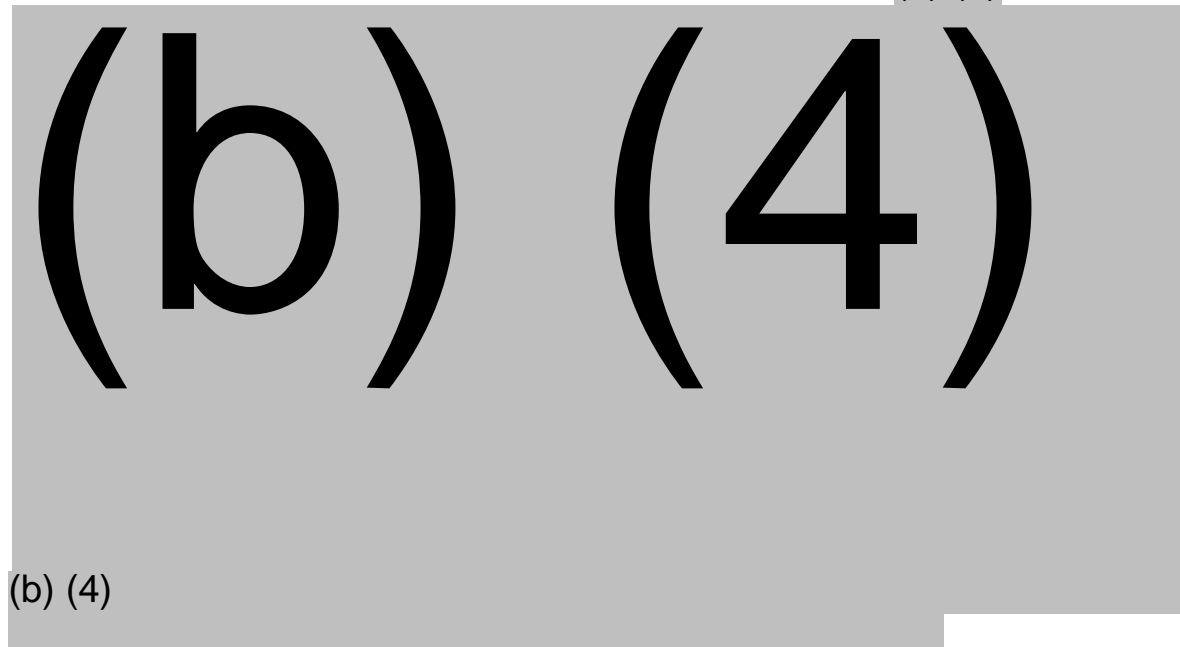


Figure 31. Axicabtagene ciloleucel potency (b) (4) under stress stability (b) (4) conditions



(b) (4)

3.2.P.8.1.4 Summary of in-use stability studies

Axicabtagene ciloleucel is to be administered by intravenous infusion immediately after thawing, with a target infusion time of 30 minutes (note that this information is also included in 3.2.P.2.6 Compatibility). To assess post-thaw stability and the effect of potential delays between thawing and infusion, in-use stability studies of thawed product held at room temperature for up to 3 hours were conducted in 3 separate studies summarized in Table 94. Scheduled tests and methods are shown in Table 95.

Table 94. Axicabtagene ciloleucel lots tested for in-use stability study

Study	Lot number	Date of manufacture	Manufacturing site	Time stored at ≤-150 °C	Time points tested
1	(b) (4)	(b) (4)	(b) (4)	6 weeks	Immediately post-thaw, and after 3 hours at room temperature
				6 weeks	
				6 weeks	
2				6 months	Immediately post-thaw, and after 3 hours at room temperature
				6 months	
				6 months	
3				~3 months	Immediately post-thaw, and after 0.5, 1, 2 and 3 hours at room temperature
				~3 months	
				~3 months	

¹ Products manufactured from healthy donor apheresis material and stored in (b) (4) bags

² Products manufactured from healthy donor apheresis material and stored in (b) (4) bags

Table 95. Test methods and acceptance criteria for in-use stability studies

Test method	Protocol acceptance criteria	Commercial acceptance criteria	Study 1	Study 2	Study 3
Appearance (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)					
Cell count (b) (4)					
Cells/ml					
% viability					
% recovery					
Cell count (b) (4)					
Cells/ml					
% viability					
% recovery					
Anti-CD19 CAR Expression (b) (4) method)					
Anti-CD19 CAR Expression (b) (4) method)					
Study 2					
Study 3					
Potency (b) (4)					
Study 1					
Study 2					
Study 3					

Test method	Protocol acceptance criteria	Commercial acceptance criteria	Study 1	Study 2	Study 3
(b) (4)	(b) (4)				

¹ Colorless to slightly yellow cell suspension. No visible leaks or damage to the bag. Port is function for sampling

² White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles

³ (b) (4) was used for all in-use stability studies as noted in Amendment 26 (response to CMC IR of 26MAY2017)

Results in all 3 studies were similar, showing that viability, potency, and (b) (4) cells continued to meet commercial acceptance after 3 hours at room temperature. Slight drops in cells/ml and cell recovery were seen for one lot in study 1, along with a (b) (4) drop in (b) (4) production (although this remained above both the protocol and commercial acceptance criterion). No changes in (b) (4) were seen in studies 1 and 2, and (b) (4) remained steady over 3 hours in studies 2 and 3.

Reviewer Comment: *In-use stability studies demonstrate that product is stable for at least 3 hours after thawing.*

(b) (4)

(b) (4)

3.2.P.8.1.6. Summary of maintenance of sterility studies

Early stability studies examined sterility of axicabtagene ciloleucel filled into (b) (4) bags, which were found to maintain sterility through 12 months when stored at $\leq -150^{\circ}\text{C}$. Additional studies have been carried out using (b) (4) engineering lots of axicabtagene ciloleucel filled into (b) (4) bags and stored at $\leq -150^{\circ}\text{C}$ for 12 (b) (4), showing that product remained sterile and that acceptance criteria for appearance were met. A study using (b) (4) lots of axicabtagene ciloleucel manufactured from donor apheresis material filled and stored at $\leq -150^{\circ}\text{C}$ in (b) (4) bags is underway (Table 96). Product appearance, container integrity, and sterility test results met acceptance criteria at 3 and 6 months, with additional testing scheduled at 12 (b) (4).

Reviewer Comment: *This is acceptable. However, because the ongoing long term maintenance of sterility studies use the commercial container closure, this material may be valuable for*

supporting stability claims. If possible, this material should also be tested for potency, viability and (b) (4) at the scheduled time points.

In Amendment 34 (Response to CMC IR of 19JUN2017), Kite Pharma agreed to add additional tests for potency, viability, and (b) (4) to the available donor-derived lots, as shown in Table 96. Note that only (b) (4) bags are available for each lot. This is acceptable.

Table 96. Stability testing of donor derived lots filled into commercial container closure

Test	Acceptance criteria	Time point (months)				(b) (4)
		LR ¹	3	6	12	
Product appearance (SOP-0317-QC3)	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no foreign visible particles	X ²	A ³ , B ⁴	A, B		(b) (4)
Container appearance (SOP-0317-QC3)	Sealed bag with sealed connections and no visible leaks or cracks				C ⁵ , D ⁶	
Sterility (TM-0007-QC3)	No growth (final read)	X	A, B	A, B	C, D	
Cell viability (TM-0005-QC3)	(b) (4)	X			C, D	
Anti-CD19 CAR expression (TM-0001-QC3)	(b) (4)	X			C, D	
Potency by (b) (4) (TM-0002-QC3)	(b) (4)	X			C, D	
(b) (4)	Report results				C, D	
(b) (4)	Report results				C, D	

¹ Lot release results are from (b) (4)

² Tested for all lots

³ Lot (b) (4) : manufactured (b) (4)

⁴ Lot (b) (4) : manufactured (b) (4)

⁵ Lot (b) (4) : manufactured (b) (4)

⁶ Lot (b) (4) : manufactured (b) (4)

3.2.P.1.7 Overall Stability conclusions

Kite Pharma is proposing an expiry date for axicabtagene ciloleucel of 12 months when stored at the recommended temperature of $\leq -150^{\circ}\text{C}$. The data provided in the BLA submission and Amendment #46 supports this, based on the following rationale and caveats:

1. Stability out to 12 months at $\leq -150^{\circ}\text{C}$ is to a large extent based on (b) (4) lots manufactured at (b) (4) and (b) (4) lots manufactured at (b) (4). Stability studies on (b) (4) healthy donor lots produced at the commercial manufacturing site (b) (4) are ongoing, with data supporting stability only out to 6 months at the time of BLA submission. To facilitate testing at multiple time points these lots were stored in (b) (4) bags rather than (b) (4) bags (the commercial container closure). Note the implicit assumptions that products stored in (b) (4) bags behave similarly to products stored in (b) (4) bags, and that healthy donor-derived axicabtagene ciloleucel is similar to patient-derived product in terms of stability.
2. Maintenance of sterility studies show that the contents of (b) (4) bags remain sterile for at least 12 months at $\leq -150^{\circ}\text{C}$. Additional studies are ongoing.

3. Accelerated stability studies indicate that product is stable to short term temperature excursions, as might be seen during transfer between (b) (4) storage and the shipping container.
4. Based on stress stability studies, (b) (4)
5. Only (b) (4) patient lots stored in (b) (4) bags have been tested to date, at 4.5, 6, 12, and (b) (4). These lots show that viability and %CD19 CAR expression are maintained out to (b) (4). However, a trend for a substantial (b) (4) drop in potency (b) (4) release) relative to lot release (b) (4) values) is seen, but lots still pass commercial acceptance criteria. Analogous (b) (4) results were seen in (b) (4) healthy donor lots in (b) (4) bags, where time 0 (b) (4) results were (b) (4) lower than at lot release (although at subsequent time points these lots showed a trend for increased potency relative to lot release). No potency drop was seen in the (b) (4) stability lots (indeed a trend for increased potency was seen for these lots) but (b) (4) testing was not performed. Due to the limited testing performed it is unclear whether the initial drop in potency seen in the patient lots is a one-time event associated with cell freezing/thawing or part of a trend. An alternative explanation could be that this reflects variability in the (b) (4) assay. However, assay validation studies demonstrate acceptable intermediate precision and repeatability and drops in potency of the observed magnitude would be out of the range of normal assay variation if the assay is performing as validated.
6. In use stability studies demonstrate that product is stable at room temperature for at least 3 hours post thawing, supporting administration of the product within the expiry period of 3 hours after thaw with a target infusion time of 30 minutes.

Reviewer Comment: The combined data from lots produced at (b) (4) supports an expiry date of 12 months when stored at $\leq -150^{\circ}\text{C}$. However, additional stability data from healthy donor lots (filled into (b) (4) and full scale (b) (4) bags) and patient lots produced at (b) (4) should be provided as it becomes available to lend further support to this 12-month expiry date. Such studies are ongoing, and Kite Pharma has committed to additional stability studies (Section 3.2.P.8.2 below).

3.2.P.8.2 Post-Approval Stability Protocol

Kite Pharma is continuing ongoing long-term and accelerated stability studies with axicabtagene ciloleucel. In addition, one lot of product (sourced from healthy donor apheresis) (b) (4) will be manufactured and filled into (b) (4) bags at the (b) (4) facility and placed on post-approval stability studies as below (Table 97).

Table 97. Post-approval stability testing for axicabtagene ciloleucel

Test	Method	Acceptance criteria	Time points (months) at -150°C					
			LR ¹	0 ²	3	6	12	(b) (4)

Test	Method	Acceptance criteria	Time points (months) at -150 °C				
			LR ¹	0 ²	3	6	12
Appearance	SOP-0317-QC3	(b) (4)	X	X	X	X	X
Container appearance	SOP-0317-QC3		X	X	X	X	X
Cell viability	TM-0005-QC3		X	X	X	X	X
Anti-CD19 CAR expression	TM-0001-QC3		X	X	X	X	X
Potency by (b) (4)	TM-0002-QC3		X	X	X	X	X

¹ Lot release (b) (4)

² After cryopreservation at ≤-150 °C

Kite Pharma will extend product expiry after satisfactory stability data have been obtained. In addition, a separate stability program will be established to confirm that the full-scale (b) (4) cryobags used for commercial product provide suitable protection from microbial contamination. One lot of donor-derived axicabtagene ciloleucel will be filled into a (b) (4) bag (b) (4), and will be tested for appearance and sterility at the end of the approved expiration period. Additional stability testing of patient lots will be performed with at least 3 separate patient lots for up to (b) (4) using the tests, acceptance criteria, and schedule described in Table 98, contingent on availability of material.

Reviewer Comment: In amendment 34 (response to the CMC IR of 19JUN2017), a proposed stability testing schedule for patient lots of axicabtagene ciloleucel filled into the commercial container closure was provided and further revised in Amendment #46 (response to Mid Cycle meeting). Kite Pharma commits to testing at least 3 independent patient lots at each time point for up to (b) (4) (Table 98 and Table 99), as circumstances permit (i.e., as patient lots become available). This is acceptable.

Table 98. Patient lot long-term stability testing plan

Test	Commercial acceptance criteria
Appearance	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no foreign particles. Sealed bag with sealed connections and no leaks or cracks
Cell count	(b) (4)
CAR expression	(b) (4)
Potency (b) (4)	(b) (4)
(b) (4)	Report results
(b) (4)	Report results
Sterility	Negative for bacteria and mold (no growth)

Table 99. Stability testing schedule for patient lots

Lot Number	Date of	Time point (months)
------------	---------	---------------------

	manufacture	LR ¹	6	12
(b) (4)	(b) (4)	X ²	NS ³	NS
		X	X	NS
		X	NS	NS
		X	NS	X
		X	NS	NS
		X	X	NS
Patient Lot TBD ⁵	TBD	X	NS	X
Patient Lot TBD	TBD	X	X	NS
Patient Lot TBD	TBD	X	NS	X
Patient Lot TBD	TBD	X	NS	NS
Patient Lot TBD	TBD	X	NS	NS
Patient Lot TBD	TBD	X	NS	NS

(b) (4)

¹ Lot release testing results from (b) (4)² X: Scheduled test point³ NS: Not scheduled⁴ Potency will be tested by (b) (4) method⁵ TBD: To be determined

Reviewer Comment: The stability testing protocols are acceptable, with the caveat that placing only a single donor-derived lot on long term stability (b) (4) will not allow statistically valid conclusions to be drawn (note that these donor-derived lots are proposed to be filled into (b) (4))

3.2.P.8.3 Stability Data

Data from final product stability studies summarized above is provided in the BLA submission and Amendment #46.

3.2.A Appendices

3.2.A.1 Facilities and Equipment

Kite Pharma's manufacturing facilities and equipment, including the (b) (4) contract facility, were reviewed by DMPQ (please see DMPQ review for additional details). Kite Pharma's procedures for qualifying and monitoring apheresis centers and treatment sites are reviewed in more detail below.

Qualification of Apheresis Centers

Qualification of an apheresis center involves completion of an onsite audit with issuance of an audit certificate and completion of onboarding activities. The elements of the audit include an assessment of the apheresis facility areas (adequately sized and controlled for receiving, preparing, collecting, shipping and storing apheresis material), apheresis equipment (brand/model used, calibration schedule and status, use and maintenance history), apheresis site staff (sufficient staff and compliance to training requirements), FACT accreditation, and documented procedures for operating equipment, training personnel, document control, COI/COC, deviations, CAPA, change control, line clearance, electronic system access control, cleaning and housekeeping, calibration of equipment, maintenance of equipment, storage and

inventory management of collection bags, and purchase and use of proper collection bags. Upon issuance of the audit certificate, apheresis center onboarding activities will be initiated. Onboarding activities include completion of Kite Pharma training for apheresis shipping materials, COI/COC and use of ATAS.

Qualification of Treatment Sites

Qualification of a treatment site involves completion of onsite audit with issuance of an audit certificate and completion of the onboarding activities. The elements of the audit include an assessment of COI/COC procedures (transfer and handling the product from delivery to treatment unit and confirmation of patient identity and correct product the time of treatment), treatment site areas (adequately sized for receiving, preparing, thawing and storing administering final product), treatment site staff (sufficient staff and compliance to training requirements), and documented site procedures for training, COI/COC, and handling final product. Upon issuance of the audit certificate, onboarding activities will be initiated. Onboarding activities include completion of Kite Pharma training for final product unpacking, storage, tracking, thawing and thawed product hold time as well as identification and reporting of product complaints and AEs.

Apheresis Center and Treatment Site Qualification Status

Based on the outcome of the initial site qualification audit, Kite Pharma Quality will designate a center/site as able to qualify or unsuitable to qualify. Upon completion of the required onboarding activities, Kite Pharma Quality will then enter site information into (b) (4) to designate the site as qualified. The qualification status of each apheresis center or treatment site will be designated by individual facility location. Only trained Kite Pharma Quality staff will have the role-based access to make EBS system updates related to site qualification status.

Monitoring

If there is evidence from the monitoring or a for-cause audit that shows the site no longer meets one or more of the qualification requirements, Kite Pharma Quality will change the site status in the EBS system to “disqualified.” The change in site status prevents future orders from being placed at the center or site and precludes apheresis or treatment procedures from being scheduled.

Qualified apheresis centers and treatment sites will be monitored by Kite Pharma Quality on a regular basis to confirm that the site has maintained its “qualified” status. The audits will occur (b) (4) until the first anniversary and (b) (4) thereafter. For-cause audits may be performed at any time if Kite Pharma Quality determines that there is a risk to product safety or quality.

Reviewer Comment: The information provided is acceptable. Kite Pharma has established controls that assure the chain of identity and chain of custody of axicabtagene ciloleucel throughout the entire supply chain, including patient apheresis material and final product handling at the treatment site.

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.2.1. Introduction and Summary

Axicabtagene ciloleucel is an autologous, gene-modified, adoptive cellular immunotherapy, precluding the use of traditional sterilization and virus clearance methods used for manufacturing

other biologics. To ensure product safety in terms of adventitious agents, procedural controls are implemented for acceptance of materials used to manufacture the (b) (4) vector and axicabtagene ciloleucel, as follows:

1. Safety testing of the (b) (4) master cell bank (MCB) and working cell bank (WCB)
2. Procedural controls, raw material controls, and safety testing of (b) (4) vector
3. Sourcing of media and reagents used in manufacture of axicabtagene ciloleucel from qualified vendors

These measures are summarized in Sections 3.2.A.2.2 and 3.2.A.2.3, below.

3.2.A.2.2. Control of adventitious agents in the production of the (b) (4) vector

The anti-CD19 CAR transgene is introduced into autologous T cells using the (b) (4) retroviral vector. The vector is produced (b) (4)

(b) (4). This MCB was extensively tested per ICH Q5 as described in Section 3.2.S.2.3.3 (see Table 9) and shown to be free from known murine viruses (from the cell line), (b) (4) (from reagents), and other endogenous and exogenous viral contaminants that could have been introduced during cell handling. Testing for retroviruses has not detected replication-competent retroviruses (RCR).

(b) (4)

Reagents used in MCB production are shown in Table 100.

(b) (4)

(b) (4)

(b) (4)

(b) (4)


(b) (4)

(b) (4)


3.2.A.2.3. Control of adventitious agents in the production of axicabtagene ciloleucel

Release tests for axicabtagene ciloleucel are described in Section 3.2.P.5 and include sterility, mycoplasma, endotoxin, and RCR.




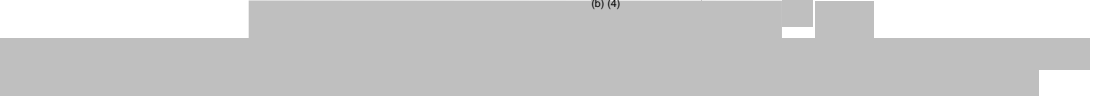
(b) (4)





|| |



(b) (4)



(b) (4)



3.2.A.2.3.2. Raw material controls

Potential sources of adventitious agents that may be introduced during manufacture of axicabtagene ciloleucel are outlined in Table 104, and include the patient-derived apheresis

material, the (b) (4) vector, and components of the culture and cryopreservation media, as well as reagents used in their manufacture.

Table 104. Potential sources of adventitious agents in axicabtagene ciloleucel manufacture

Material	Manufacturer	Component	Component manufacturer	Species of component origin	Country of component origin	CoA provided
Patient apheresis material	N/A ¹	N/A	N/A	Human	USA	N
(b) (4)						
Human Serum Albumin ⁶	(b) (4) ²	N/A	N/A	Human	USA	Y

¹ N/A – not applicable

² HSA is FDA licensed product

³ (b) (4) may be from either supplier

⁴ (b) (4) is produced in (b) (4) in secondary manufacturing

⁵ (b) (4)


⁶ Used in final product formulation

Apheresis material quality is primarily controlled through qualification of collection sites, with (b) (4) contamination tested at lot release. Any viruses present in

the apheresis material would be patient-derived (i.e. the patient is already infected with them). As this is autologous material, it represents a low risk in terms of adventitious agents.

The (b) (4) vector is extensively tested as described in Sections 3.2.S.4 (Control of drug substance (b) (4) and 3.2.A.2.2.

The (b) (4)



The quality of other reagents used in manufacture of axicabtagene ciloleucel is assessed by Kite Pharma through review of supplier certificates of analysis. All reagents have been tested for adventitious agents and subjected to viral inactivation procedures as described in detail in Section 3.2.S.2.3.1 (Control of source and starting materials of biological origin (axicabtagene ciloleucel, Kite Pharma)). As human derived material is used, a theoretical risk of TSE (primarily Creutzfeld-Jakob disease [CJD]) contamination cannot be ruled out, but the likelihood of this is extremely low and no cases of CJD transmission from human albumin have been identified.

Reviewer Comment: These measures for control of adventitious agents are acceptable.

3.2.A.3 Novel Excipients

There are no novel excipients in the axicabtagene ciloleucel drug product.

3.2.R Regional Information (U.S.A.)

3.2.R.1 Executed Batch Records

Executed batch records were included in the BLA. The information contained in the batch records are summarized throughout the BLA in the form of tables and graphs. Executed batch records confirm the data used in the tables and graphs.

3.2.R.2 Method Validation Package

Kite Pharma provided summaries of the detailed method protocols and summaries of the validation reports in 3.2.S.4 Control of Drug Substance (b) (4) 3.2.S.4 Control of Drug Substance (Kite Pharma, Inc, axicabtagene ciloleucel) and 3.2.P.5 Control of Drug Product. The method validation packages were reviewed in the relevant sections above.

3.2.R.3 Comparability Protocols

Comparability data were reviewed in the BLA in regards to opening of the new (b) (4) in 2016 (see 3.2.S.2.6 Manufacturing Process Development). In the future Kite Pharma is planning to (b) (4)

(b) (4). Currently (b) (4) workstations have been qualified in Suite (b) (4) (Room (b) (4) and (b) (4) additional workstations in Suite (b) (4) (Room (b) (4) are expected to be qualified for production of commercial product at launch (see DMPQ review) (b) (4) contains (b) (4) additional production suites (room (b) (4) and room (b) (4)). To bring these suites into service Kite Pharma is not proposing to perform a comparability study. Instead Kite Pharma will: 1) Complete equipment qualification, 2) Qualify the room by performing static and dynamic environmental monitoring, 3) Complete aseptic process validation runs, and 4) Change control systems used to document actions.

Reviewer Comment: Kite Pharma plans (b) (4)