CBER CMC BLA Review Memorandum

BLA STN 125703

TECARTUS
brexucabtagene autoleucel

Reviewers
Graeme Price, Ph.D. CBER/OTAT/DCGT/GTIB
Jakob Reiser, Ph.D. CBER/OTAT/DCGT/GTIB
Tal Salz, Ph.D. CBER/OTAT/DCGT/GTB

1. BLA#: STN 125703

2. APPLICANT NAME AND LICENSE NUMBER: Kite Pharma, Inc.; License # 2064

3. PRODUCT NAME/PRODUCT TYPE

Non-proprietary/Proper/USAN:	brexucabtagene autoleucel
Proprietary name:	TECARTUS
Company codename:	KTE-X19
UNII Code:	4MD2J2T8SJ
NDC Codes:	71287-219-01 (bag), 17287-219-02 (cassette)

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological Category: CD19-directed genetically modified autologous T cell immunotherapy

Dosage form: Cell suspension

Strength/Potency: 2×10^6 anti-CD19 CAR T cells/kg (maximum allowable dose of 2×10^8 anti-CD19 CAR T cells based on patient weight of ≥100 kg) in a nominal volume of 68 ml

Route of administration: Intravenous infusion

Indication: Treatment of adult patients with relapsed/refractory (r/r) mantle cell lymphoma (MCL)

5. MAJOR MILESTONES

Initial IND submission (BB-IND-16675):	09OCT2015
Orphan drug designation for MCL:	28APR2016
CMC type C meeting (BB-IND-16675):	12APR2018
Breakthrough Therapy Designation for r/r MCL (BB-IND-16675):	15JUN2018
Initial multidisciplinary BTD meeting for r/r MCL (BB-IND-16675):	21SEP2018
Format/content of BLA type B meeting (BB-IND-16675):	23APR2019
REMS type B meeting:	19SEP2019
Pre-BLA type B meeting (BB-IND-16675):	15NOV2019
BLA 125703 submission date:	11DEC2019
BLA 125703 filing meeting:	23JAN2020
BLA 125703 mid-cycle meeting:	26MAR2020
BLA 125703 late-cycle meeting:	28MAY2020
BLA 125703 target date:	27JUL2020
BLA 125703 PDUFA action date:	10AUG2020

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Graeme Price Ph.D. CBER/OTAT/DCGT/GTIB	Drug Substance (b) (4) Vector): Sections 3.2.S.6 and 3.2.S.7; Drug Substance (Kite Pharma, Inc., KTE-X19): Sections 3.2.S.1, 3.2.S.2 (except 3.2.S.2.6), 3.2.S.3, 3.2.S.6, and 3.2.S.7; Drug Product: Sections 3.2.P.1, 3.2.P.2, 3.2.P.4, 3.2.P.7, and 3.2.P.8; Appendices 3.2.A.1 and 3.2.A.2; Module 1 A (Environmental Assessment) and B (Labeling); Modules 4 and 5 (Analytical Procedures and Assay Validation)
Jakob Reiser Ph.D. CBER/OTAT/DCGT/GTIB	Drug Substance (b) (4) Vector): Sections 3.2.S.1, 3.2.S.2, 3.2.S.3, 3.2.S.4, and 3.2.S.5
Tal Salz Ph.D. CBER/OTAT/DCGT/GTB	Drug Substance (Kite Pharma, Inc. KTE-X19): Sections 3.2.S.2.6, 3.2.S.4, and 3.2.S.5; Drug Product: Sections 3.2.P.5 and 3.2.P.6
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) GMP CD28 Pure monoclonal antibodies
Sukhanya Jayachandra, Ph.D. CBER/OTAT/DCGT/CTB	3.2.S.2.3 Consult review for (b) (4)
Elizabeth Lessey-Morillon, Ph.D. CBER/OTAT/DCGT/CTB	3.2.S.2.3 Consult review for (b) (4) T cell expansion basal medium, T cell expansion supplement, and (b) (4)

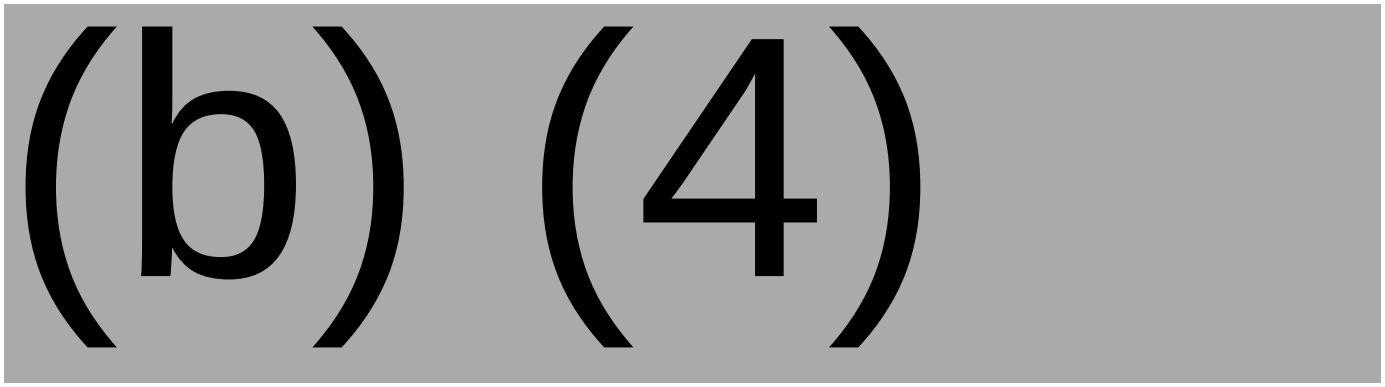
7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
None Requested	N/A	N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
11DEC2019	STN 125703/0.0	BLA Original Submission
19DEC2019	STN 125703/0.5	Labeling for apheresis material
22JAN2020	STN 125703/0.8	Response to DMPQ IR of 14JAN2020
27JAN2020	STN 125703/0.9	Response to CMC IR of 17JAN2020
29JAN2020	STN 125703/0.10	Response to DMPQ IR of 24JAN2020
30JAN2020	STN 125703/0.11	Response to CMC IR of 17JAN2020
07FEB2020	STN 125703/0.14	Response to CMC IR of 30JAN2020
14FEB2020	STN 125703/0.16	Response to CMC IR of 07FEB2020
24FEB2020	STN 125703/0.18	Response to CMC IR of 07FEB2020
24FEB2020	STN 125703/0.19	Response to CMC IR of 14FEB2020
09MAR2020	STN 125703/0.24	Response to CMC IR of 28FEB2020
10MAR2020	STN 125703/0.25	Response to CMC IR of 05MAR2020
11MAR2020	STN 125703/0.28	Response to DMPQ IR of 26FEB2020
23MAR2020	STN 125703/0.31	Response to CMC IR of 13MAR2020
27MAR2020	STN 125703/032	Confirmation of non-proprietary name
13APR2020	STN 125703/0.37	Response to CMC IR of 03APR2020
17APR2020	STN125703 /0.38	Response to CMC IR of 10APR2020 Confirmation of KTE-X19 lot release criteria
22APR2020	STN125703/0.39	Response to CMC IR of 14APR2020: Updated UNII
18MAY2020	STN125703/0.45	Updated PPQ lot stability data
22MAY2020	STN125703/0.48	Revised package labels
19JUN2020	STN125703/0.49	Response to CMC IR of 11JUN2020 Confirmation of dose specification and shelf-life
24JUN2020	STN125703/0.52	Revised Prescribing Information and labeling

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



10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The CMC review team concludes that the manufacturing process for brexucabtagene autoleucel yields a product of sufficiently consistent quality, and recommends approval of this Biologics License Application.

Brexucabtagene autoleucel (referred to throughout this review as KTE-X19) is intended for treatment of relapsed/refractory Mantle Cell Lymphoma (MCL) and consists of autologous CD19-specific chimeric antigen receptor (CAR) expressing T cells generated by in vitro transduction with a retrovirus vector (b) (4) encoding the CAR transgene but lacking all other elements required for productive replication. KTE-X19 is manufactured from autologous apheresis material that is positively selected for (b) (4) cells using a (b) (4) to enrich T cells and remove circulating B cells, tumor cells, and monocytes. The enriched T cell population is activated by stimulation with immobilized anti-CD3 monoclonal antibodies (mAb) and soluble anti-CD28 mAb in the presence of interleukin (IL)-2 for 2 days. Activated T cells are transduced with the (b) (4) vector for approximately (b) (4) until the required dose is met. Cells are then harvested, washed and formulated in an infusible cryopreservation solution (b) (4) sodium chloride (b) (4) human serum albumin (HSA), (b) (4) CryoStor® (b) (4) to provide a dose of 2.0×10^6 anti-CD19 CAR T cells/kg of patient body weight, with a maximum allowable dose of 2.0×10^8 anti-CD19 CAR T cells for patients weighing ≥100 kg in a 68 ml nominal volume. Formulated KTE-X19 is filled into infusion bags and cryopreserved at ≤ -150°C for up to 12 months, as supported by stability data. One infusion bag provides one dose of KTE-X19. Each patient apheresis provides (b) (4) doses of KTE-X19 per manufacturing run. When possible, excess (b) (4) . The drug product contains no preservatives other than cryopreservation medium. The product is shipped frozen in a (b) (4) , with the product bag contained in a protective aluminum cassette. The product bag is stored in vapor phase liquid nitrogen until required, when it is thawed and infused within 3 hours, as supported by stability data.

Manufacturing and quality

Two drug substances (DS) are involved in the manufacture of KTE-X19: The (b) (4) retroviral vector, and patient apheresis material-derived CAR T cells. The (b) (4) CD19-specific antibody single chain variable fragment (scFv) fused to human CD28 and the CD3ζ intracellular domain under

control of the (b) (4) This vector is identical to that used in the manufacture of axicabtagene ciloleucel (YESCARTA®), a similar autologous anti-CD19 CAR T cell product approved for relapsed/refractory diffuse large B cell leukemia (DLBCL) in 2017 under BLA 125643. The key difference between axicabtagene ciloleucel and KTE-X19 is that the KTE-X19 process uses a T cell enrichment step (which removes circulating tumor cells from apheresis material) that is absent from the axicabtagene ciloleucel process. The reduction in non-T cell populations as a result of T cell selection necessitates the use of an anti-CD28 mAb in addition to the anti-CD3 mAb to provide co-stimulation of T cells; this is not required for axicabtagene ciloleucel manufacture. The manufacturing processes for axicabtagene ciloleucel and KTE-X19 are otherwise similar.

(b) (4)

The KTE-X19 manufacturing process begins with collection of apheresis material from patients at qualified apheresis centers. Chain of identity/chain of custody (COI/COC) procedures are established once the apheresis material has been collected. These procedures involve tracking the patient-specific material at each step in the manufacturing process from apheresis collection through to infusion of the final drug product (DP), and are critical to maintain control of intermediates and product to ensure that each patient receives the correct, autologous lot of KTE-X19. Apheresis material is shipped to the (b) (4) facility, where it is inspected and, if acceptable, the KTE-X19 manufacturing process is initiated. Apheresis material is processed via washing, followed by selection of T cells on the basis of (b) (4) using the (b) (4) device and (b) (4) reagents. Enriched T cells are then activated using anti-CD3 and anti-CD28 mAbs in the presence of IL-2. (b) (4) Activated T cells are then transduced with the (b) (4) vector and expanded in culture until sufficient anti-CD19 CAR T cells are available to meet dose requirements (b) (4) The culture is then harvested, washed and concentrated to form the KTE-X19 (b) (4).

The KTE-19 (b) (4) is formulated to make the DP with (b) (4). The DP is formulated in saline/HSA/CryoStor® (b) (4) infusible cryopreservation solution; each dose is comprised of a fixed number of anti-CD19 CAR T cells calculated based on viable cell count and (b) (4) T cells (determined by (b) (4) for CAR expression) and patient body weight. Formulated DP is filled into 510(k)-cleared

cryopreservation/infusion bags by (b) (4) methods, with each bag containing one dose in a 68 ml nominal volume. One (b) (4) doses of KTE-X19 are produced from each manufacturing run. Filled DP bags are examined for appearance, then cryopreserved using a (b) (4) freezer and stored at ≤ -150°C in vapor phase liquid nitrogen until lot release testing is complete. Released DP is then shipped frozen to qualified treatment sites for administration back to the same patient who donated the manufacturing source material.

KTE-X19 is manufactured in a (b) (4) raw materials and reagents that meet acceptable quality standards. Human and animal derived raw materials are appropriately controlled to ensure absence of microbial, including viral, contaminants. All DS and DP manipulations are logged in the COI/COC system, which is adequate to establish and maintain control of the product throughout the process. Samples for lot release testing are collected at the appropriate stages during manufacture: Mycoplasma, (b) (4) endotoxin, and sterility testing samples are drawn from each filled DP bag; product appearance is assessed in filled bags prior to cryopreservation. Lot release test methods are suitably validated (except for the appearance method, which is a qualified compendial assay) and product specifications are adequate to ensure product quality and consistency.

The 510(k)-cleared cryopreservation/infusion bags used as the container closure system for KTE-X19 are originally intended for use with blood products. These bags have been appropriately tested in compatability, extractables/leachables, container integrity, and stability studies and have no impact on KTE-X19 quality or safety.

KTE-X19 Stability
Drug product stability under long term storage conditions (≤ -150°C) has been assessed using a limited number of clinical KTE-X19 lots filled into the commercial cryopreservation bags, and for healthy donor-derived KTE-X19 lots filled into small scale bags. While viability and potency are maintained for up to (b) (4) months in these studies, conclusions regarding (b) (4) (CAR expression) are confounded due to changes in qualification of assay reagents introduced while the stability study was ongoing. Additional long-term stability studies using healthy donor-derived process performance qualification (PPQ) lots filled into the commercial cryopreservation bags are ongoing. Based on the results of these studies to date, the shelf-life of KTE-X19 stored at ≤ -150°C should be set at 12 months.

B. RECOMMENDATION

I. APPROVAL

This biologics license application (BLA) provides an adequate description of the manufacturing, testing, and characterization of the new drug product brexucabtagene autoleucel. The CMC review team has concluded that the manufacturing process, and associated testing and control measures, is capable of generating a product with consistent quality attributes. This information satisfies the CMC requirements for biological product licensure under the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products.

Manufacturing facilities

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

- Kite Pharma, Inc. (b) (4)

CBER Lot release
Brexucabtagene autoleucel has been deemed exempt from CBER lot release testing or protocol review.

Post-Marketing Commitments
None.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Graeme Price, Ph.D. Review Committee Chair, Research Microbiologist CBER/OTAT/DCGT/GTIB		
Jakob Reiser, Ph.D. Research Biologist, CBER/OTAT/DCGT/GTIB		
Tal Salz, Ph.D. Biologist CBER/OTAT/DCGT/GTB		
Denise Gavin, Ph.D. Branch Chief, Gene Therapy Branch CBER/OTAT/DCGT/GTB		
Steven Oh, Ph.D. Deputy Director, Division of Cellular and Gene Therapies CBER/OTAT/DCGT		
Raj Puri, M.D. Ph.D. Director, Division of Cellular and Gene Therapies CBER/OTAT/DCGT		

Review of CTD

Table of Contents

Module 3

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

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

This section reviewed by JR

3.2.S.1.1 Nomenclature

The company code for the retroviral vector used in the manufacture of Brexucabtagene autoleucel (KTE-X19) is (b) (4) . A USAN/INN name will not be available for the (b) (4) vector.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

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3.2.S.2 Manufacture (Kite Pharma, Inc., KTE-X19)

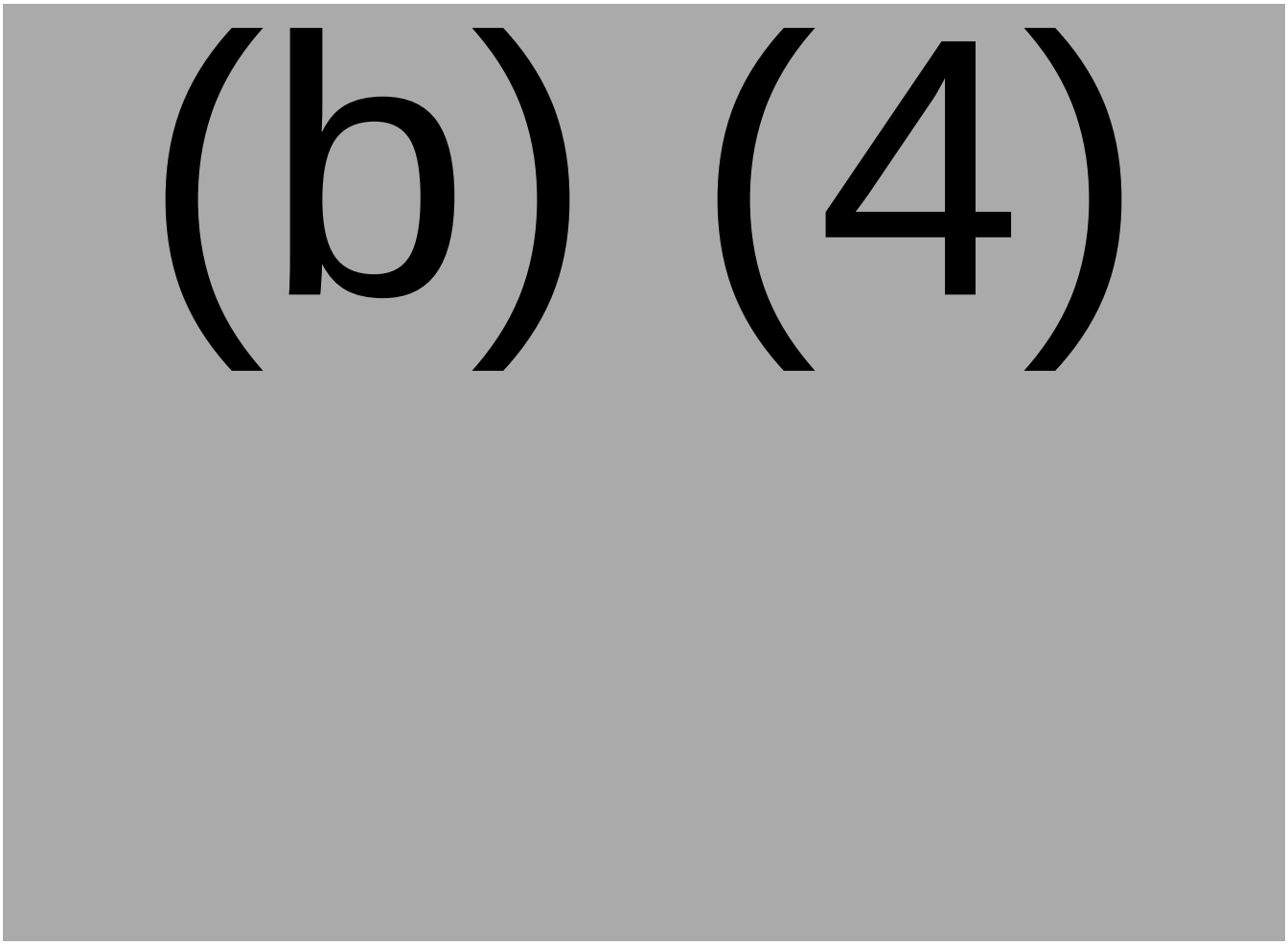
This section reviewed by GEP

3.2.S.2.1 Manufacturer(s) (Kite Pharma, Inc., KTE-X19)

The manufacturer of KTE-X19 is Kite Pharma, Inc., and raw material testing is performed by various contractors, as outlined in Table 38.

Table 38. KTE-X19 manufacturing and testing facilities

Facility	Responsibility
Kite Pharma, Inc. (b) (4) FEI: (b) (4) DUNS: (b) (4)	Manufacture, control, and storage of KTE-X19 Final product release testing per specifications
Kite Pharma, Inc.	Raw material testing



3.2.S.2.2 Description of Manufacturing Process (Kite Pharma, Inc., KTE-X19)
The manufacturing process for KTE-X19, known as the XLP process, is outlined in Figure 11. Briefly, T cells are isolated from patient apheresis material by positive selection with (b) (4) and then activated by incubation with (b) (4) anti-CD3 mAbs and (b) (4) anti-CD28 mAbs in medium supplemented with IL-2. There is an optional (b) (4)

After (b) (4), the activated T cells are transduced with the CAR-encoding (b) (4) retroviral vector for (b) (4), then expanded in culture for a minimum of (b) (4) prior to harvest, wash and concentration. The manufacturing process is (b) (4) Therefore, the review of DS manufacture includes all steps up to and including the final wash and concentration step. The DP review (3.2.P DRUG PRODUCT) includes details of final product formulation and filling.

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

(b) (4)

[1] (b) (4)

(b) (4)

3.2.S.2.6 Manufacturing Process Development (Kite Pharma, Inc., KTE-X19)

This section reviewed by TS

Manufacturing Changes:

Several manufacturing changes were implemented during clinical investigation (BB-IND-16675). Characterization or comparability studies were performed to evaluate these changes. A summary of key manufacturing changes is provided in Table 50.

Table 50. Summary of significant changes in the manufacturing process

BB-IND-16675 Amendment #	Date submitted	Description of change	Purpose of change
SN 0008	30MAR2016	Additional data to support use of (b) (4) T cells	(b) (4)
SN 0012	14JUN2016	Addition of second clinical manufacturing facility (b) (4)	To allow manufacture, control, storage and release testing of final production at (b) (4)
SN 0116	16AUG2017	Addition of clinical manufacturing facility (b) (4)	To allow manufacture, control, storage and release testing of final production at (b) (4)
		Change in (b) (4)	To reduce operational complexity by eliminating (b) (4) requirements
SN 0131	06NOV2017	Update of final product release specification	Addition of appearance, identity by (b) (4), impurities (gentamicin and BSA), and (b) (4) on final product release specification

BB-IND-16675 Amendment #	Date submitted	Description of change	Purpose of change
SN 0195	10AUG2018	Change in (b) (4) during T cell activation step	To allow an acceptable (b) (4) during the T cell activation process
		Addition of an alternative formulation and filling process	To introduce the (b) (4) formulation and filling system for (b) (4) processing of DP prior to cryopreservation
SN 0243	01MAR2019	Addition (b) (4)	(b) (4)
		Addition of alternative primary container closure system	To allow formulation and fill in an alternative cryostorage bag for distribution of final product
SN 0290	20AUG2019	Addition of RDMC[1] for KTE-X19 clinical production	To allow manufacture, control, storage, and release testing of final product at RDMC
SN 0319	09DEC2019	Extension of apheresis shelf-life stability	To allow longer storage of apheresis starting material
		Removal of manufacturing sites (b) (4) for clinical production	To remove facilities where final product is no longer manufactured

[1] RDMC: Kite Research, Development and Manufacturing Center, Santa Monica, CA

Reviewer comment: *Information in Table 50 was provided in Amendment #9 (response to CMC IR of 17JAN2020), received 27JAN2020. Note that the Amendment numbers in the originally submitted version are incorrect; the BIRAMS database was cross-checked and the correct amendment numbers are provided above. These changes are summarized below:*

- (b) (4) *of the enriched T cells after* (b) (4) *was added as an optional step. Characterization studies supporting this change are described later in this Section.*
- *The addition of* (b) (4) *manufacturing facility was proposed in BB-IND-16675 Amendment #116. Comparability data between* (b) (4) *using a* (b) (4) *study design was reviewed under that Amendment and found acceptable.* (b) (4) *is intended for the commercial manufacturing.* (b) (4) *were removed and are not applicable to the commercial manufacturing of KTE-X19. 42 of 69 ZUMA-2 clinical lots in the batch analyses were manufactured in the commercial manufacturing facility* (b) (4)*.*
- *Addition of optional* (b) (4) *filling system was proposed in BB-IND-16675 Amendment #195. Results from characterization are reviewed in Section 3.2.P.2.3 Manufacturing Process Development.*
- *Addition of an alternate container closure system was proposed in BB-IND-16675 Amendment #243, and supporting studies were reviewed there. These studies are also described and reviewed in Sections 3.2.P.2.4 Container Closure System, 3.2.P.2.5 Microbiological Attributes, and 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data.*
- *The addition of* (b) (4) *in the* (b) (4) *formulation step was proposed in BB-IND-16675 Amendment #243. Characterization studies supporting this change are reviewed under that amendment and in Section 3.2.P.2.3 Manufacturing Process Development.*

Characterization Studies:
The KTE-X19 manufacturing process is based on the FDA-approved YESCARTA® manufacturing process with the following major changes to account for the difference in the incoming apheresis material:

- (b) (4)

Risk Assessment
Risk analysis of process parameters was based on the product and process knowledge from YESCARTA®, and from KTE-X19 process development and clinical manufacturing. The goal of the characterization studies was to identify high risk process steps where further risk mitigation and controls are needed to establish consistent commercial manufacturing. Process parameters having an impact on a critical quality attribute within the characterized range were classified as critical process parameters.

(b) (4)

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

3.2.P DRUG PRODUCT

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

This section reviewed by GEP

KTE-X19 consists of autologous T cells that have been selected on the basis of (b) (4), genetically modified ex vivo to express a CAR targeting CD19 on the surface of malignant B cells and expanded in culture. These transduced T cells are formulated in cryopreservation medium suitable for infusion and are supplied to the clinical site frozen at ≤ -150°C in cryostorage bags. Each KTE-X19 final product bag contains a dose of 2.0×10^6 anti-CD19 CAR T cells/kg of patient weight in a nominal 68 ml volume. Table 64 lists the components of KTE-X19.

Table 64. Components of KTE-X19

Component	Quantity per bag (68 ml nominal volume)	Function	Quality standard
Anti-CD19 CAR T cells	2×10^6 anti-CD19 CAR T cells/kg (maximum allowable dose 2×10^8 anti-CD19 CAR T cells based on patient weight ≥100 kg)	Active ingredient	See section (3.2.P.5.1)
CryoStor® (b) (4)	(b) (4)	(b) (4)	BB-MF-(b) (4)
Sodium chloride (b) (4)	(b) (4)	(b) (4)	(b) (4)
Albumin (human), (b) (4)	(b) (4)	(b) (4)	(b) (4)

3.2.P.2 Pharmaceutical Development

This section reviewed by GEP

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The active substance of KTE-X19 consists of $CD3^+$ T cells that have been transduced with an anti-CD19 CAR-encoding retroviral vector. The T cell subset composition varies from patient lot to patient lot, and a small percentage of CD3 negative cells may also be present in KTE-X19 (see Section 3.2.S.3.1 Elucidation of Structure and Other Characteristics). A summary of key characteristics from ZUMA-2 patient lots of KTE-19 is provided in Table 65.

(b) (4)

3.2.P.2.1.2 Excipients

The following excipients are present in KTE-X19:

- Sodium chloride, (b) (4) This provides (b) (4) to KTE-X19. Final concentration in KTE-X19 is (b) (4)
- Human albumin (HSA), (b) (4) This functions as a (b) (4). Final concentration in KTE-X19 is (b) (4) HSA)
- CryoStor® (b) (4): This is the cryopreservative used in KTE-X19. Final concentration in KTE-X19 is (b) (4)

See Section 3.2.P.4 for additional information on excipients.

3.2.P.2.2 Drug Product

This section reviewed by GEP

3.2.P.2.2.1 Formulation Development

As the manufacturing process for KTE-X19 is based on that for YESCARTA® and the products are similar, results from YESCARTA® process development and characterization studies served as the basis for defining KTE-19 process parameters.

Reviewer comment: *As formulation process parameters for KTE-X19 (HSA and CryoStor® (b) (4) concentrations, bag type, fill volume, and mixing parameters) are identical for YESCARTA® and KTE-X19 these results are directly applicable for both products.*

KTE-X19-specific studies were performed to assess the performance of the (b) (4) viable cell density range, and (b) (4) hold time for final product in CryoStor® (b) (4) medium. The formulation parameters studied and conclusions are summarized in Table 66 and described below.

Table 66. Summary of formulation parameters, characterized, proven and acceptable ranges, and criticality assessment

Process parameter	Characterized range	Proven acceptable range	Parameter classification
HSA concentration in final formulation	(b) (4)	(b) (4)	Non-critical
CryoStor® (b) (4) concentration in final formulation	(b) (4)	(b) (4)	Non-critical
Final formulation (b) (4) time	(b) (4)	(b) (4)	Non-critical
Range of viable cell density in final formulation	(b) (4)	(b) (4)	Critical
Formulation method	(b) (4)	(b) (4)	Non-critical
(b) (4) recovery procedures	(b) (4)	(b) (4)	Non-critical
Hold time for final product in (b) (4)	(b) (4)	(b) (4)	Non-critical

The concentrations of HSA and CryoStor® (b) (4) used in final product formulation were evaluated for YESCARTA®. Viability and post-thaw recovery of formulated CAR T cells were assessed in (b) (4) CryoStor® (b) (4) at HSA concentrations of (b) (4) Across this range, no differences were seen the following parameters:

- (b) (4)

Variability in the volume/final concentration of CryoStor® (b) (4) used for formulation was assessed for YESCARTA® by (b) (4) Across this range of CryoStor® (b) (4) concentrations, no impacts were seen on the following parameters:

- (b) (4)

- (b) (4)

The (b) (4) time following addition of CryoStor® (b) (4) was evaluated for YESCARTA® during (b) (4) (as used in the (b) (4) fill process) by assessing (b) (4)

The impact of final formulation cell concentration was assessed for KTE-X19 using product bags from (b) (4) healthy donor lots and (b) (4) patient lots which had been formulated over a range of cell concentrations from (b) (4) These products were stored in vapor phase LN_2 for up to (b) (4), thawed, (b) (4), and monitored for viability and cell growth over (b) (4) as shown in Figure 20 and Figure 21, respectively.

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

Reviewer comment: *The cryopreservation process development studies performed for YESCARTA® are directly applicable to KTE-X19 as the same container closures, formulation, and fill volumes are used. These studies have been previously reviewed and found acceptable under BLA 125643.*

3.2.P.2.2.2 Overages

There are no overages for KTE-X19.

3.2.P.2.2.3 Physicochemical and Biological Properties

See Section 3.2.S.3.1

3.2.P.2.3 Manufacturing Process Development

The only DP manufacturing process development studies conducted were formulation/filling studies, which are reviewed in section 3.2.P.2.2.1 Formulation Development

3.2.P.2.4 Container Closure System

Two primary container closure systems are used interchangeably for KTE-X19; (b) (4) bags are 510(k)-cleared (b) (4) cryostorage bags intended for storage of blood and blood products. These bags are fully described in 3.2.P.7 Container Closure System.

Reviewer comment: (b) (4) *bags, along with a smaller version of the* (b) (4) *bag used during clinical development studies (including long-term and accelerated stability studies), are described in the YESCARTA® BLA OS (BLA 125643/0) and BLA supplement #121 (BLA 125643/216) and have been found acceptable. As YESCARTA® and KTE-X19 are highly similar products, and the formulation processes are identical, bag characterization studies (including shipping studies, extractables and leachables studies and integrity testing reviewed under 3.2.P.7 Container Closure System) performed for YESCARTA® are applicable to KTE-X19.*

3.2.P.2.5 Microbiological Attributes
The capacity for the primary container closure system (b) (4) bags) to provide a barrier against (b) (4) has been qualified by an appropriate container closure integrity testing using a (b) (4) -based method. This testing is reviewed in 3.2.P.7 Container Closure System.

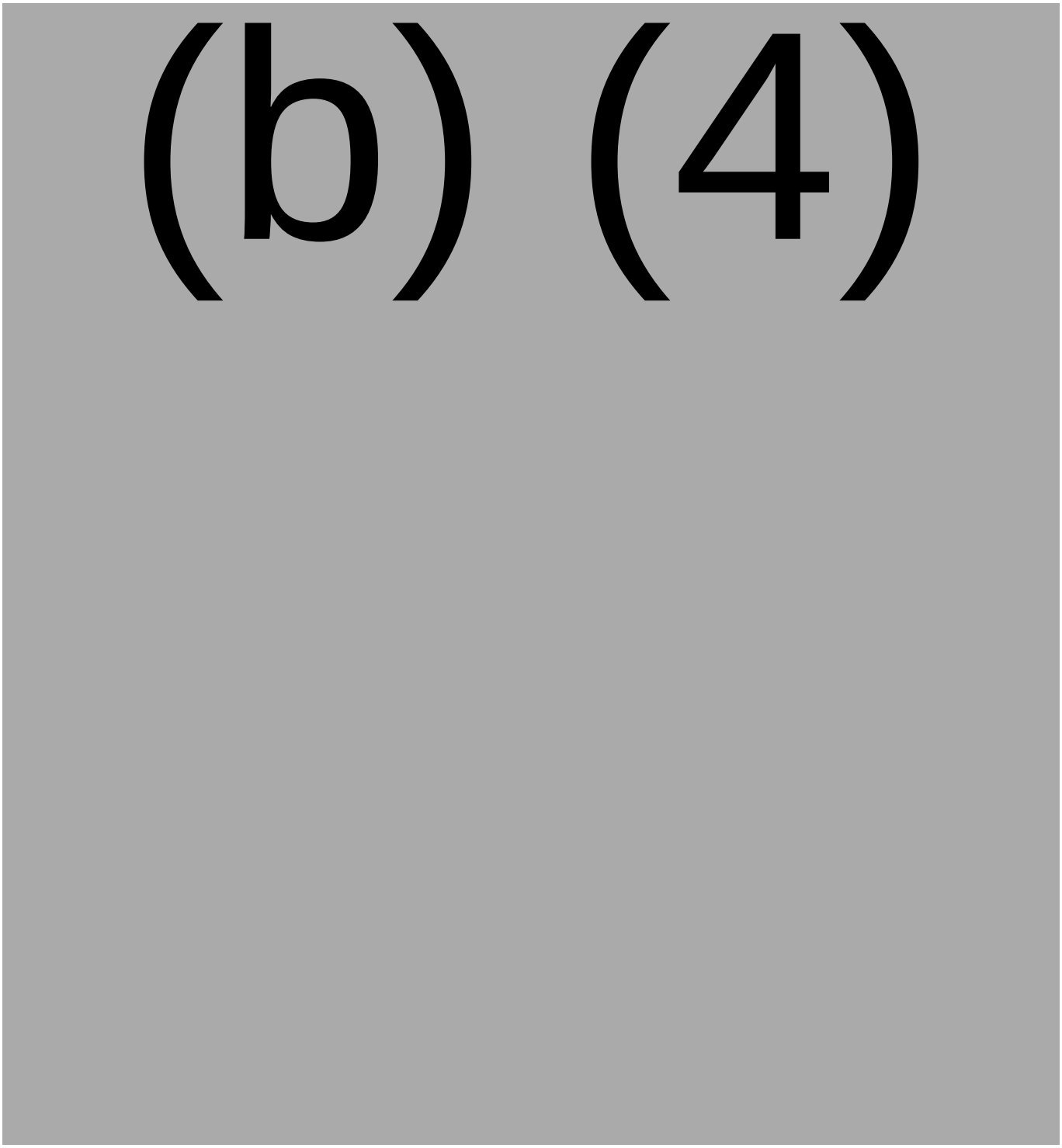
3.2.P.2.6 Compatibility
Not applicable. There are no reconstitution diluents or dosage device included in the KTE-X19 final drug product.

Overall Reviewer's Assessment of Section 3.2.P.2:
Information provided in Section 3.2.P.2 is acceptable, with no deficiencies identified. There are no concerns.

3.2.P.3 Manufacture
This section reviewed by GEP
3.2.P.3.1 Manufacturer(s)
The KTE-X19 DP is manufactured by Kite Pharma, Inc. as outlined in Section 3.2.S.2.1 and Table 38.

3.2.P.3.2 Batch Formula
All components in the dosage form of KTE-X19, their amounts on a per batch basis, and the relevant quality systems are described in Table 64 (3.2.P.1 Description and Composition of the Drug Product).

3.2.P.3.3 Description of Manufacturing Process
The KTE-X19 manufacturing process proceeds directly from DS harvest wash to formulation, as outlined in Figure 28.



3.2.P.3.3.2.1 Formulation

KTE-X19 is formulated with (b) (4) NaCl, (b) (4) HSA, and CryoStor® (b) (4) stock solutions. Samples for (b) (4) testing are taken prior to harvest wash (Section 3.2.S.2.2.2.12 Harvest wash and concentration), with samples for (b) (4) determination taken after the harvest wash. The volume required to achieve the target dose (Table 71) is calculated using (b) (4), patient weight, and viable cell concentration with a fixed final product volume (68 ml). Depending on the patient

weight and (b) (4), sufficient cells may be available to fill (b) (4) final product bags. Each bag contains one patient dose.

Table 71. Target dose calculation

Patient weight	Dose for MCL indication
<100 kg	2×10^6 $CD3^+$ CAR^+ T cells/kg
≥100 kg	2×10^8 $CD3^+$ CAR^+ T cells (flat dose)

- (b) (4)

(b) (4)

(b) (4)

- (b) (4)

- **Inspection and labeling**

After filling, the aseptically sealed KTE-X19 final product bags (together with labels and COI/COC documentation) are transferred out of the manufacturing suite (via a pass through) to the visual inspection station and examined for color and visible particulates. Final product labels are then affixed to the bags and they are placed in pre-labeled aluminum cassettes for transfer to a (b) (4) freezer.

- **Cryopreservation and storage**

The cassette(s) containing the final product bag(s) are placed in a (b) (4) freezer (b) (4) and frozen according to a defined profile (Table 73). This profile has an (b) (4) to maintain high viability of the cryopreserved cells.

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.3:
The KTE-X19 DP formulation, filling, and cryopreservation processes are acceptable. No deficiencies were identified and there are no concerns.

3.2.P.3.4 Controls of Critical Steps and Intermediates

As manufacturing of KTE-X19 is a (b) (4) DP. Control of critical steps for KTE-X19 DS manufacture is described in 3.2.S.2.4 Controls of Critical Steps and Intermediates. DP formulation process parameters, derived from manufacturing process development studies (see 3.2.P.2.3 Manufacturing Process Development), are summarized in Table 74.

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.4:
Information describing control of DP critical steps is acceptable as submitted. No deficiencies were identified and there are no concerns.

3.2.P.3.5 Process Validation and/or Evaluation
This section reviewed by GEP
3.2.P.3.5.1 Manufacturing Process Validation
Reviewer comment: *Information in this section is provided in Section 3.2.S.2.5.1 of the BLA submission, but is reviewed here as validation was performed on the complete process from DS manufacture through DP filling and cryopreservation.*

Validation of the KTE-X19 manufacturing process was performed using a life cycle approach consisting of 3 stages: process design, process performance qualification (PPQ), and continued/ongoing process verification (OPV).

A risk-based assessment of the KTE-X19 process was performed, where process risks and knowledge gaps were studied systematically to define proven acceptable ranges and classifications (critical or non-critical) for process parameters (see Sections 3.2.S.2.6 Manufacturing Process Development (Kite Pharma, Inc., KTE-X19) and 3.2.P.2.3 Manufacturing Process Development). Understanding of the process gained from the process design stage was enhanced with information gained from full scale clinical manufacturing lots. The resulting information was used to establish process parameter operating ranges and process expectations for KTE-X19 PPQ. After PPQ was completed, the OPV program was established to ensure that the commercial manufacturing process remains in a state of control. A monitoring and review program has been established to define, collect, analyze, and respond to trends in process performance and product quality data.

(b) (4)

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

(b) (4)

(b) (4)

Reviewer comment: *This is acceptable. There are no product office or DMPQ concerns with aseptic process validation.*

3.2.P.3.5.2 Final product shipping validation

Validation of final product transportation conditions was performed by laboratory-based simulations to qualify the shippers and testing under actual shipping conditions. These studies were performed for YESCARTA®, but are applicable for KTE-X19 due to similarity of the product and identical packing and shipping parameters. Experience with clinical shipments of KTE-X19 is also described.

- **Laboratory-based dry vapor liquid nitrogen shipper qualification**

The (b) (4) used for final product transportation were loaded (per commercial shipping procedures) with (b) (4) bags containing a surrogate final product (b) (4) and tested (b) (4)

(b) (4)

(b) (4)

Reviewer comment: *Updated information (including report QR-1769) was provided in Amendment #19 (response to CMC IR of 14FEB2020) received 24FEB2020 and is acceptable. This* (b) (4) *testing represents the worst case scenario for abuse in transit. The cassettes with* (b) (4) *inserts are acceptable.*

(b) (4)

(b) (4)

Reviewer comment: *Laboratory-based temperature maintenance testing indicates that the shippers are qualified to maintain an internal temperature of ≤ -150°C for cargo shipments of up to* (b) (4) *in duration. Note that commercial shipments will include a temperature monitoring device so any temperature excursions can be noted and evaluated.*

- **In-use shipping validation**

Studies were performed to demonstrate that YESCARTA® shipped in the dry vapor LN_2 shipper remained at the appropriate temperature, maintained physical integrity, and met viability and potency specifications. The studies (summarized in Table 89) are directly applicable to KTE-X19 as the viability specification, shipping temperature, and bag integrity are the same as YESCARTA®, and the potency specification is wider for KTE-X19 (b) (4) than for YESCARTA® (b) (4)

Reviewer comment: *Clarifications regarding the chosen durations/distances for* (b) (4) *shipping studies were provided in Amendment #19 (response to CMC IR of 14FEB2020) received 24FEB2020 and are acceptable.*

(b) (4)

All (b) (4) shipments of YESCARTA® met protocol acceptance criteria and commercial release specifications for viability and potency and results were similar to unshipped control samples held at ≤ -150°C.

Reviewer comment: *These shipping validation studies are adequate to support the proposed KTE-X19 shipping methods.*

- **KTE-X19 shipping experience**

All clinical shipments of KTE-X19 (beginning 28JAN2016, ending 26FEB2019) were reviewed. From (b) (4) KTE-X19 lots shipped during this timeframe, there were no temperature excursions or broken bags. In addition, (b) (4) YESCARTA® product bag out of (b) (4) commercial shipments (b) (4) has lost physical integrity during shipment.

Reviewer comment: *This information is supportive of the acceptability of the packing and transportation processes.*

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

(b) (4)

(b) (4)

The final product shipping validation studies are based on YESCARTA® and are acceptable. Information to clarify minor details was requested during the review cycle and responses were acceptable, as outlined above. There are no concerns regarding product packing or shipping.

3.2.P.4 Control of Excipients

This section reviewed by GEP

3.2.P.4.1 Specifications

Excipients used in the final formulation of KTE-X19 are shown in Table 90. Each lot of excipient is received, inspected, sampled, tested, and dispositioned according to written procedures.

Table 90. Excipients used in manufacture of KTE-X19

Excipient	Vendor/Supplier	Grade
Albumin (Human) (b) (4)	(b) (4)	(b) (4)
(b) (4) Sodium Chloride Injection	(b) (4)	(b) (4)
CryoStor® (b) (4)	(b) (4)	(b) (4)

Specifications for CryoStor® (b) (4) are provided in Table 91. This is a defined cryopreservation medium, all components of which are (b) (4)-grade or compendial materials (when available) purchased from approved suppliers.

(b) (4)

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures
Compendial test procedures for Albumin (Human) (b) (4) Sodium Chloride, injection comply with (b) (4) . Testing for CryoStor® (b) (4) uses compendial methods, as described in the (b) (4) Master File (BB-MF-(b) (4). However, (b) (4) non-compendial tests on this material are performed by Kite Pharma:

- Appearance testing (for color and visible particulates) is performed by appropriately trained personnel using visual inspection (b) (4) per (b) (4)
- DMSO content is assessed by (b) (4) and standard grade DMSO as a reference material. (b) (4) to calculate DMSO content. This assay has been validated per (b) (4) requirements, as summarized in Table 92.

(b) (4)

3.2.P.4.4 Justification of Specifications
Test methods and acceptance criteria for Albumin (Human) (b) (4) Sodium Chloride, Injection meet (b) (4) . requirements, and both products are approved for human use. CryoStor® (b) (4) specifications are justified in BB-MF-(b) (4) and testing is performed for CQAs relevant for use as a cryopreservative for KTE-X19 (including

(b) (4)

3.2.P.4.5 Excipients of Human or Animal Origin

Albumin (human) (b) (4) supplied by (b) (4) All lots are derived from plasma donations individually tested and found non-reactive for HBsAg, anti-HIV1/2 antibodies, antibodies against HAV, HBV, and HCV, and parvovirus B19, using FDA approved tests. Each plasma pool was tested and found negative for HBsAg, HIV1/2 antibody, and HCV RNA (b) (4). Donors are also tested and found non-reactive in a serologic test for syphilis. All lots are also tested for sterility and endotoxin.

There are no components of human origin in CryoStor® (b) (4), and the only animal origin component is (b) (4). Certifications have been provided from the supplier to ensure that the lactobionic acid is free of transmissible spongiform encephalopathy agents. See also Section 3.2.A.2 Adventitious Agents Safety Evaluation.

3.2.P.4.6 Novel Excipients

There are no novel excipients used in KTE-X19.

Overall Reviewer's Assessment of Section 3.2.P.4:
The excipients used in KTE-X19 manufacture are identical to those for YESCARTA®. Information reading these excipients was acceptable as submitted, and no IRs were required during the review cycle. There are no concerns regarding excipients.

3.2.P.5 Control of Drug Product

This section reviewed by TS with revisions to dose by GEP

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

The release specifications for KTE-X19 and the justification for each specification are provided in Table 93 below. Detailed justification is outlined below the table. Where appropriate, KTE-X19 samples for release testing are taken (b) (4) of the final product container in order to conserve final product volume and appropriate dose. Therefore, release test samples are taken at the (b) (4) steps as indicated in Table 93 and Figure 32 below. A total of (b) (4) ZUMA-2 KTE-X19 lots manufactured using the proposed commercial process in the ZUMA-2 study at a target dose of 2.0×10^6 CAR^+ T cells/kg were evaluated in setting release specifications. (b) (4) of those (b) (4) lots were administered at the maximum dose level. All (b) (4) lots were included in the analyses justifying specifications. Outlier datapoints were not included in the analyses. Additionally, a total of (b) (4) KTE-X19 final product lots manufactured from donor apheresis material during Process Performance Qualification (PPQ) campaign were tested to confirm the specifications. To justify the specification for (b) (4), % cell viability, and (b) (4) release, the FDA performed an analysis of these product quality attributes by correlating the data with clinical outcomes (AE and response rate). The results of these FDA analyses are displayed using box and whisker plots (Figures 33-38). The specification range was determined based on (b) (4) (for (b) (4) or

(b) (4) tolerance intervals at 95% confidence/ (b) (4) coverage of the manufacturing data.

Table 93. KTE-X19 final product specifications

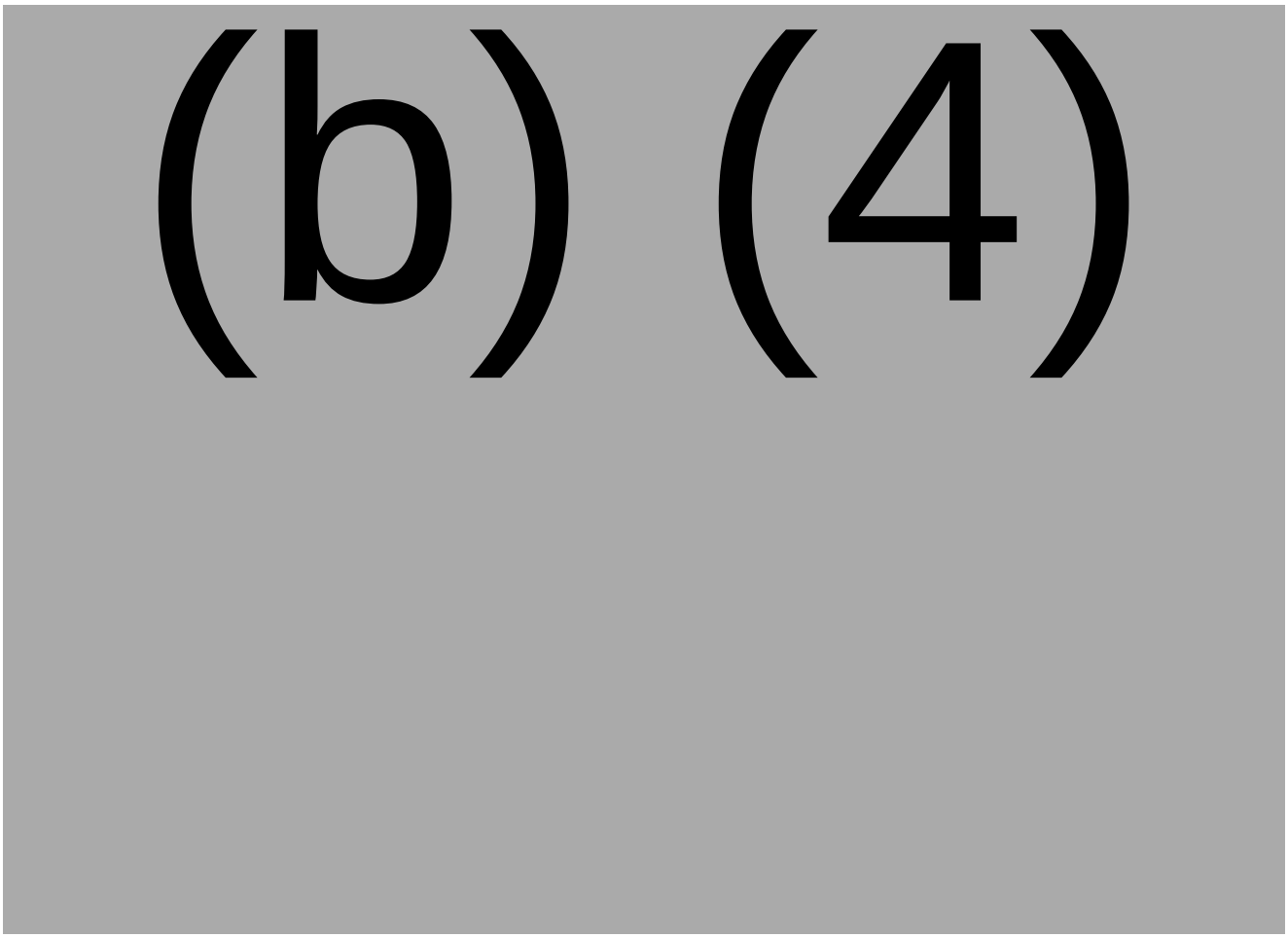
Attribute	Test	Sample Point (Process Step)	Analytical Procedure	Acceptance Criteria
Appearance	Visual Appearance Inspection	Inspection and Labeling	Visual Inspection (SOP-00624)	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles[1]
Identity	(b) (4)	Formulation	(b) (4) to detect the scFv heavy chain variable region, linker and CD28 sequences (CAR: (b) (4)	(b) (4)
Dose[1]	Viable Cell Count/Anti-CD19 CAR Expression	N/A[2]	(b) (4))	2×10^6 Anti-CD19 CAR T cells/Kg (Maximum allowable dose 2×10^8 Anti-CD19 CAR T cells based on patient weight ≥ 100 kg[1]
Potency	Cell Viability	(b) (4)	(b) (4)	(b) (4)
	Anti-CD19 CAR Expression	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Safety	Mycoplasma	(b) (4)	(b) (4)	Negative[1]
	Sterility	Formulation	(b) (4)	Negative[1]
	Endotoxin	Formulation	(b) (4)	(b) (4)
	(b) (4)	Formulation	(b) (4)	(b) (4)

Abbreviations: CAR, chimeric antigen receptor; (b) (4)

[1] Specification is identical to YESCARTA®

[2] Dose is calculated based on patient weight, viable cell concentration and (b) (4)

Reviewer comment: *Final product specifications were revised during the review cycle, as outlined below. Revised specifications were communicated to the applicant (CMC IRs of 10APR2020 and 11JUN2020) and confirmed in revisions to BLA Sections 3.2.P.5.1 (Specifications) and 3.2.P.5.6 (Justification of Specifications) as detailed in Amendment #38, received 17APR2020, and in Sections 3.2.P.1 (Description and Composition of the Drug Product), 3.2.P.3.2 (Pharmaceutical Development), 3.2.P.5.1 (Specifications) and 3.2.P.5.6 (Justification of Specifications) as detailed in Amendment #49, received 19JUN2020. The revised specifications are acceptable*.



Appearance
The acceptance criterion has been established based on observation of clinical lots in the final container closure. This test is performed on the product in final container.

Identity (b) (4)
This test is performed on the product in the final container and is specific for the (b) (4) gene and hence can identify cells transduced with the (b) (4) vector. However, it cannot distinguish between KTE-X19 and YESCARTA® which will be manufactured in the same facility using the same vector.
Reviewer comment: *A potential concern is that the* (b) (4) *-based identity test cannot distinguish between YESCARTA® and KTE-X19 because the same* (b) (4) *is used to manufacture both products. A potential risk is that if apheresis material from a MCL patient is erroneously manufactured via the YESCARTA® process (which unlike the KTE-X19 process does not select out circulating tumor B cells) transduced tumor B cells could be present in the final product. Kite is aware of this issue and in Amendment #14 (response to CMC IR of 31JAN2020), received 07FEB2020, justified the lack of a product-distinguishing identity test by noting that validated COI/COC processes have been established (described in detail and reviewed in Section 3.2.A.1.3. Chain of Identity/Chain of Custody (COI/COC)). These procedures ensure the correct product is being manufactured. Following discussions with CBER/OCBQ, reliance on COI/COC*

procedures to compensate for the lack of a product-distinguishing identity test is acceptable in this instance.

Dose

The dose of KTE-X19 is a calculated based on patient body weight, measurements of viable cell concentration, and (b) (4) . The (b) (4) is determined based on (b) (4) Samples for cell viability are taken (b) (4) . Various studies supported consistent cell viability throughout the process, including post-thaw cell viability. Therefore, the sampling time for cell viability reasonably represents the final product. KTE-X19 is manufactured to a dose of 2×10^6 anti-CD19 CAR T cells per kg patient weight (maximum allowable dose: 2×10^8 anti-CD19 CAR T cells for ≥100 kg patients).

Reviewer comment: *The original proposed acceptance criterion of (b) (4) anti-CD19 CAR T cells per kg was consistent with the dose ranges defined in multiple clinical studies of KTE-X19 across different indications. However, in the ZUMA-2 study (b) (4) of lots met the target dose of 2×10^6 anti-CD19 CAR T cells per kg; (b) (4) of these (b) (4) lots were administered at the maximum dose of 2×10^8 anti-CD19 CAR T cells per kg. Given the high rate at which the target dose could be met in the ZUMA-2 study, it appears that manufacture of KTE-X19 to consistently meet a dose of 2×10^6 anti-CD19 CAR T cells per kg is feasible. After discussions with the clinical review team, and assessment of the doses administered in the ZUMA-2 study, it was concluded that due to the limited sample size there is insufficient data to confirm efficacy for doses below 2×10^6 anti-CD19 CAR T cells per kg. Therefore, the commercial dose for the MCL indication should be set at 2×10^6 anti-CD19 CAR T cells per kg or a maximum dose of 2×10^8 anti-CD19 CAR T cells per kg for patients ≤ 100kg. This revised dose specification was communicated to the applicant 11JUN2020 and confirmed in revisions to sections 3.2.P.1 (Description and Composition of the Drug Product), 3.2.P.3.2 (Pharmaceutical Development), 3.2.P.5.1 (Specifications) and 3.2.P.5.6 (Justification of Specifications) as described in Amendment #49, received 19JUN2020.*

Cell viability

The % cell viability is measured (b) (4) . The % cell viability data from (b) (4) KTE-X19 ZUMA-2 clinical lots ranged between (b) (4) and is normally distributed. Cell viability in (b) (4) lots was (b) (4), with one outlier (b) (4), which was excluded from the analysis to estimate the lower specification limit (see Figure 33). Acceptance criteria for viability were established using one-sided tolerance interval with (b) (4) proportion coverage at the 95% confidence level, resulting in a specification limit of (b) (4) based on data from (b) (4) lots.

Reviewer comment: *Information aiding assessment viability criteria was submitted in Amendment #19 and Amendment #31 (received 24FEB2020 and 23MAR2020, respectively). An independent analysis of the relations between cell viability and clinical outcome was done by the Agency and the results are presented in Figure 33. The cell viability data was not logit transformed as was originally proposed by Kite because the raw % viability data appears to be normally distributed without transformation. There was no statistically significant association between cell viability and disease response or AEs. The viability specification was calculated as (b) (4) based on one-sided tolerance intervals at 95% confidence/(b) (4) coverage of viability data from (b) (4). This value of (b) (4) was rounded up to (b) (4) (the same specification as for YESCARTA®).*

(b) (4)

Potency (b) (4) *production)*

(b) (4)

(b) (4)

(b) (4)

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

Mycoplasma
To maximize detection, samples for mycoplasma testing are taken at the (b) (4) Mycoplasma testing is performed using the (b) (4) as described in section 3.2.P.5.2. The acceptance criterion is "Negative" for the presence of mycoplasma, in accordance with regulatory and safety requirements ((b) (4) and 21 CFR 610.30). All (b) (4) KTE-X19 clinical lots and (b) (4) PPQ lots have conformed to the specification.

Sterility
The sample for culture sterility testing is taken from the final container. Sterility testing is performed using the (b) (4) as described in section 3.2.P.5.2. The specification for Sterility is "No growth," in accordance with regulatory and safety requirements. All (b) (4) KTE-X19 clinical lots and (b) (4) PPQ lots have conformed to the specification.

Endotoxin
The sample for endotoxin testing is taken from the final container. Endotoxin testing is performed using (b) (4) method as described in section 3.2.P.5.2. An acceptance criterion of (b) (4) has been established for Endotoxin to ensure that patients weighing (b) (4) or above, receiving a 68 ml infusion of KTE-X19, will be exposed to endotoxin levels below the (b) (4) threshold described in (b) (4) (i.e., (b) (4) limit).

(b) (4)

Retention samples
Kite developed a (b) (4) sample retention plan, as indicated in Table 94, below. All (b) (4) are cryovials at ≤ -150°C. (b) (4) samples are designated solely as final product retained samples, and represent the minimum samples available in the event of a product complaint investigation. (b) (4) samples are retained for different purposes, but if available could be used for post-distribution investigations.

(b) (4)

(b) (4)

Reviewer comment: *The sample retention plan is acceptable. The minimum amount of product retained for each lot is* (b) (4) *which should reasonably be sufficient to investigate post-distribution quality issues. Additional samples from each product will most likely be available* (b) (4) *in the event that* (b) (4) *is insufficient material for the specific investigation.*

Reviewer's assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:
The sampling plan and testing adequately control the final product dose, purity, potency and safety while conserving final product needed for proper patient dosing. Based on independent analyses of manufacturing data and clinical outcomes conducted by the Agency, acceptable specification limits were set as indicated in Table 93.
Note that residual impurities levels are not measured as part of final product release testing; this is acceptable (see Section 3.2.S.3.2 Impurities for more details).

The absence of RCR testing on the final cellular product is acceptable based on current FDA guidance (Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-Up, January 2020: An appropriate product sample retention program is in place, allowing retrospective analysis of RCR if needed. The following points are also relevant:

1. *The vector and* (b) (4) *cells are tested appropriately for RCR (see 3.2.S.4.2 Analytical Procedures); All vector lots to date have been negative for RCR.*
2. *The* (b) (4) *vector is designed to reduce the likelihood of generating RCR by:*
   (b) (4)
3. *Recombination of vector packaging plasmids and cellular DNA leading to RCR has not been reported with the current viral vector systems in the literature (Adham and Bear, 2012. Mol Ther 20: 246-249. Replication-competent retroviruses in gene-modified T cells used in clinical trials: is it time to revise the testing requirements?). In addition, The MCB and WCB used for* (b) (4) *vector production were tested are found negative for RCR.*
4. *KTE-X19 clinical lots were tested and found negative for RCR when cell expansion extended beyond* (b) (4) *days post-transduction* (b) (4) *YESCARTA® lots manufactured between NOV2017 and NOV2018 have been negative for RCR.*

Note that Kite also proposes in a PAS to discontinue (b) (4) *-based RCR testing at lot release for YESCARTA®. This review is pending.*

During the review cycle, specifications for viability and (b) (4) were revised based on (b) (4) clinical lots of KTE-X19 shown to be safe and effective for the MCL indication in the ZUMA-2 study, as outlined above. FDA assessment of these lots resulted in revision of the viability specification to (b) (4) and the (b) (4) specification to (b) (4) all other specifications were acceptable as submitted. Revised specifications were communicated to the applicant on 10APR2020, and agreed to in Amendment #38, received 17APR2020. The revised final product specifications are acceptable.

3.2.P.5.2 Analytical Procedures
All final product release testing is done at the manufacturing facility (b) (4)

Visual appearance (SOP-00624)
The appearance test for KTE-X19 is a 100% manual visual inspection performed by qualified inspectors per SOP-00624. This assay was not validated, but follows compendial reference chapters (b) (4) and conforms to their control strategies, including assurance of (b) (4) . The test consists of a visual inspection of the final container integrity, and inspection of product clarity, color, and presence of cellular debris or visible particulate matter against a black and white backgrounds. All bags are inspected without magnification one at a time. Results are confirmed for failed bag(s) by a second qualified inspector and reviewed prior to product disposition.
Reviewer comment: *This is acceptable.*

Identity (b) (4)
The (b) (4) identity assay employs quantitative (b) (4) to detect the (b) (4) in KTE-X19 final product. Identity is confirmed when (b) (4) is amplified by (b) (4), above the limit of quantitation. Please see description of (b) (4) testing for additional information.
Reviewer comment: *The assay can identify the product, but (as discussed above) it cannot distinguish between the YESCARTA® product and the KTE-X19 product which are manufactured in the same facility.*

(b) (4)

(b) (4)

Reviewer comment: *this assay is acceptable.*

Potency (b) (4)
Potency is measured by demonstrating that KTE-X19 can be (b) (4)

Reviewer comment: *This assay is acceptable. Of note, although it is commonly used as a potency assay for CAR T cell products it does not correlate with clinical response.*

Dose determination (b) (4)
The dose is based on the number of viable anti-CD19 CAR-positive T cells per kg of patient body weight. (b) (4) analytical methods used for KTE-X19 dose determination: viable cell count (b) (4) ; described below) and the percentage of anti-CD19 CAR T cells ((b) (4) The dose is 2×10^6 anti-CD19 CAR T cells/kg (Maximum allowable dose 2×10^8 anti-CD19 CAR T cells for patients weighing ≥100 kg). The dose is calculated as follows:

- (b) (4)

Reviewer comment: *this assay is acceptable.*

Anti-CD19 CAR expression (b) (4)
Anti-CD19 CAR expression on the surface of T cells is assessed to determine (b) (4) The anti-CD19 CAR is detected with a (b) (4)

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

- (b) (4)

Cell Viability (b) (4)

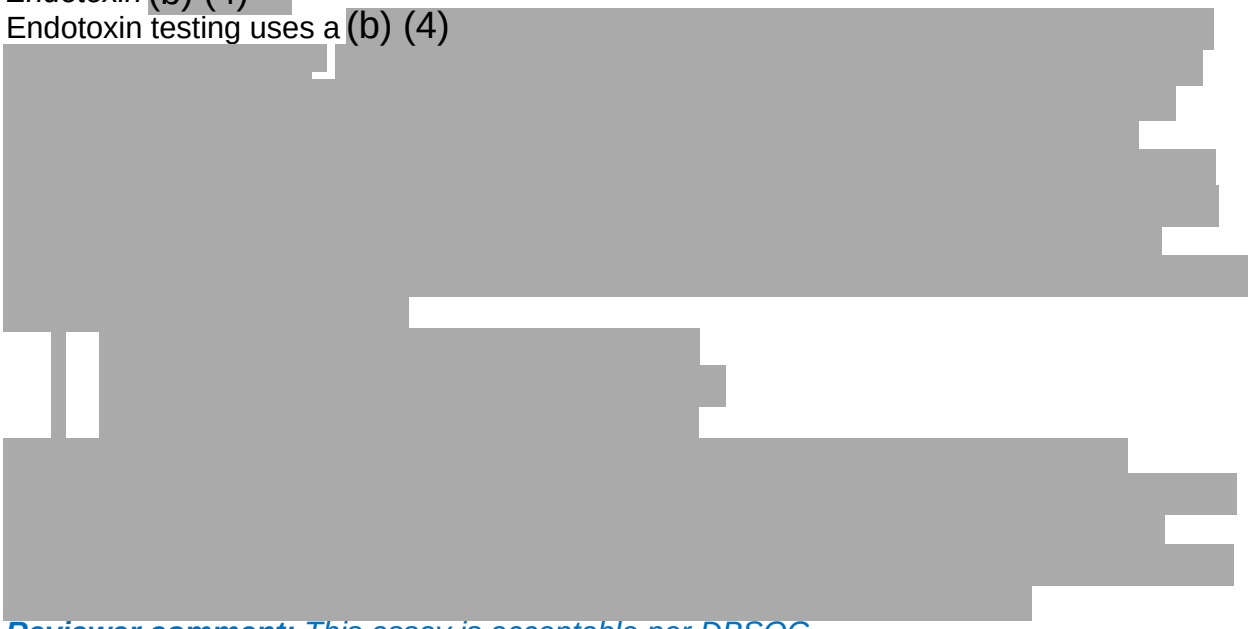
Reviewer comment: *This assay is acceptable.*

Sterility (b) (4)

Rapid sterility testing is performed using the (b) (4)

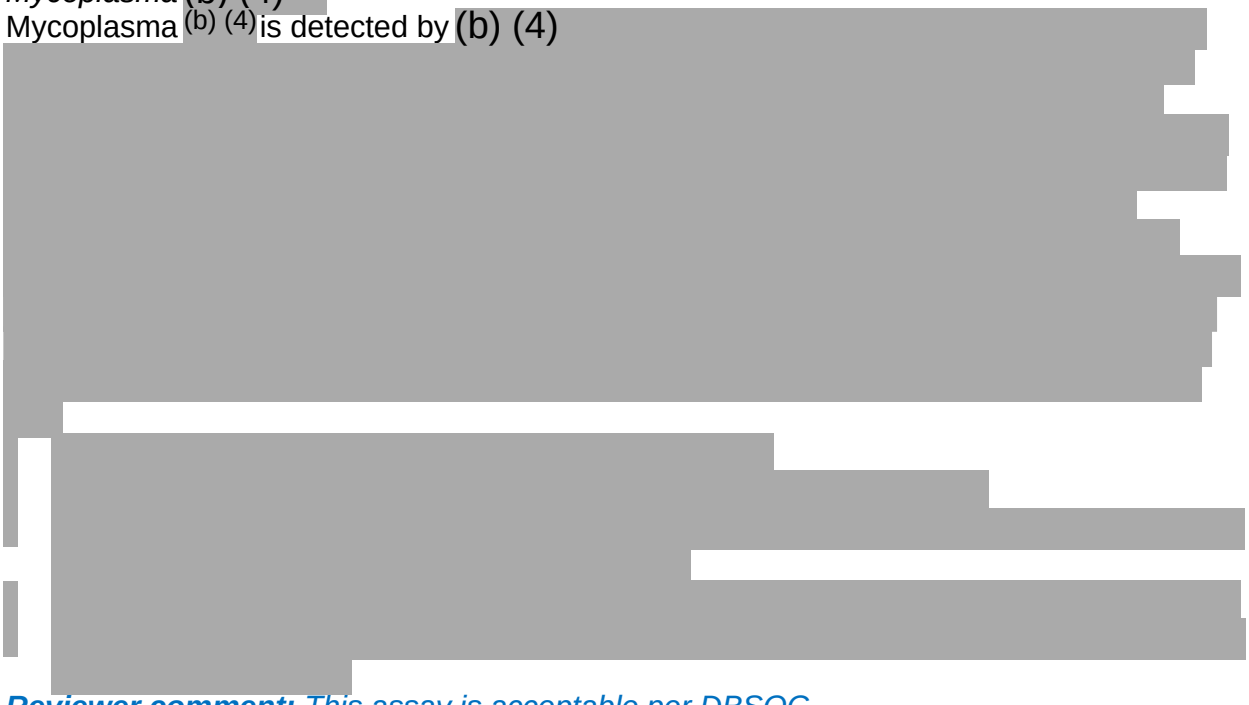
Reviewer comment: *This assay is acceptable per DBSQC.*

Endotoxin (b) (4)
Endotoxin testing uses a (b) (4)



Reviewer comment: *This assay is acceptable per DBSQC.*

Mycoplasma (b) (4)
Mycoplasma (b) (4) is detected by (b) (4)



Reviewer comment: *This assay is acceptable per DBSQC.*

3.2.P.5.3 Validation of Analytical Procedures
The YESCARTA® and KTE-X19 final products are very similar and are formulated identically. The same release testing methods are used for both products. Kite has previously validated those methods for YESCARTA® (BLA 125643) per ICH Q2 (R1).

Additional validation studies using KTE-X19 product samples were performed to supplement the YESCARTA® validation studies because there are manufacturing process differences that could potentially impact method performance. Justifications for selecting specific validation parameters are listed in Table 95. The same validation acceptance criteria were used for both YESCARTA® and KTE-X19 validation studies, but the number of replicates differed at times. Each method validation is summarized in a table which includes both the previously reviewed YESCARTA® validation and supplemental KTE-X19 validation parameters (see Table 96 - 98, below). As assay reagents, sampling handling, and method execution are identical for YESCARTA® and KTE-X19, robustness and reagent stability were not re-assessed with KTE-X19 samples.

Reviewer comment: *Review of the validation of sterility, mycoplasma, and endotoxin was conducted by CBER/OCBQ/DBSQC. Per the DBSQC reviewer memo, Kite's* (b) (4) *mycoplasma test method using* (b) (4) *performed on the KTE-X19 drug product (DP) were validated in accordance with* (b) (4) *respectively, by demonstrating the methods are suitable under the actual conditions of use. Kite demonstrated these test methods provide assurance of tested matrix safety and purity that is equal to, or greater, than the assurance of the current compendial methods. Also, sterility and mycoplasma using culture metho*(b) (4) *and bacterial endotoxin* (b) (4) *DP) test methods were qualified in accordance with* (b) (4) *respectively, by demonstrating they are suitable under the actual conditions of use.*

Table 95. Summary of supplemental validation of analytical procedures for KTE-X19 release testing

Method	Assessed Supplemental Parameters	Justification and Rationale	Method Validation Report Number
Appearance (visual)	N/A	Only SOP provided since this is a compendial method not affected by product matrix	N/A
(b) (4)	Repeatability Intermediate Precision	(b) (4) step could be impacted by the KTE-X19 formulation matrix. Method was assessed for listed parameters to ensure precision of the (b) (4) result remained consistent with YESCARTA® validation	QR-0835
Potency (b) (4)	Repeatability Intermediate Precision	Formulation matrix could impact interaction of KTE-X19 with (b) (4) cells. Method was assessed for the listed parameters to ensure precision of sample results remained consistent with the YESCARTA® validation	QR-0278
Anti-CD19 CAR Expression (b) (4))	Linearity Accuracy Precision Sensitivity	Method was assessed for KTE-X19 to ensure that process changes do not impact linear range or precision of reported results established in YESCARTA® validation	QR-0259

Method	Assessed Supplemental Parameters	Justification and Rationale	Method Validation Report Number
Viability and cell concentration (b) (4)	Specificity Accuracy Linearity Precision Intermediate Precision	Cell count and viability are tested throughout the process and used for dose calculation. Validation of these parameters in the context of the KTE-X19 process is required to account for any impact to the method with this product	QR-0435
Sterility (b) (4)	Specificity	Growth of the specified organisms in presence of final product matrix is required to establish method suitability for testing KTE-X19	REP-18947 QR-0437 QR-0731 QR-1106 QR-1181
Endotoxin (b) (4)	Maximum Valid Dilution (MVD) Repeatability Sample Qualification	Qualification of KTE-X19 samples required to ensure method is not impacted by process changes and accurate results can be determined within final product sample MVD	QR-1116
Mycoplasma (b) (4)	Accuracy Specificity Precision	(b) (4) could be impacted by KTE-X19 formulation matrix. Method was assessed for listed parameters to ensure precision and accuracy of the (b) (4) result remained consistent with YESCARTA® validation	QR-0500

Reviewer comment: *Method validation is acceptable. Validation studies were adequately supplemented using KTE-X19 samples where appropriate.*

(b) (4)

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

(b) (4)

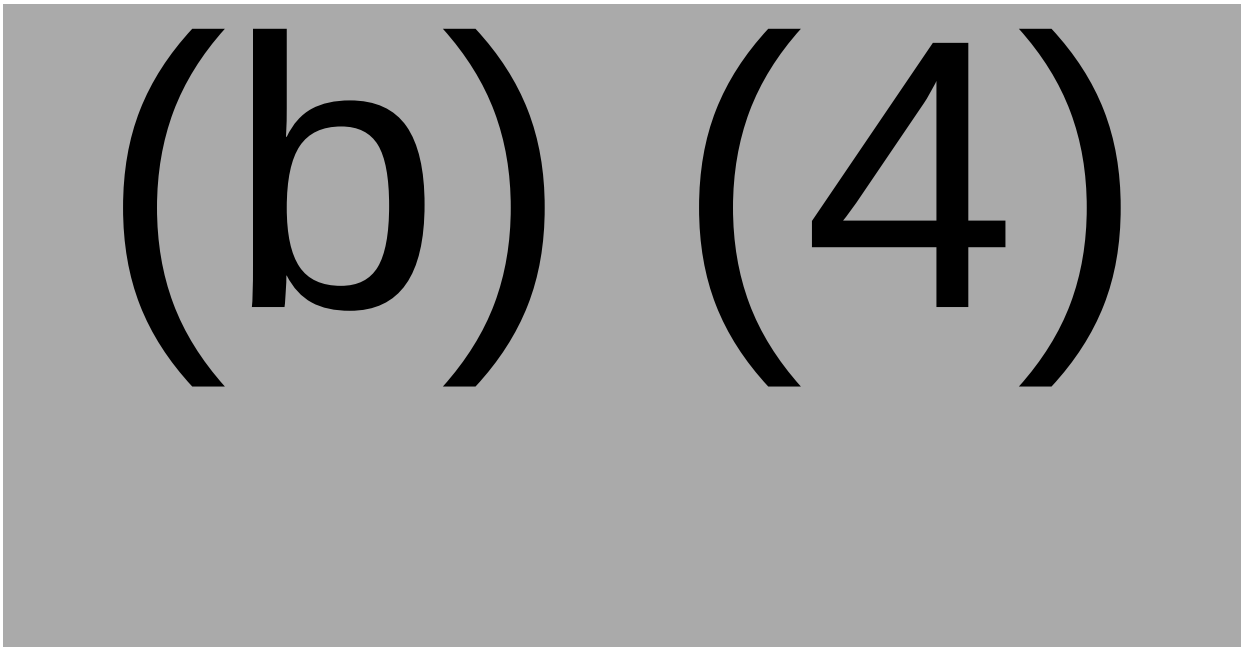
Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:
The analytical methods and the validation of the analytical methods are acceptable based on the information provided in the original BLA submission and responses to information requests as indicated in the reviewer comments. Kite relied on validation data generated using YESCARTA samples as well as KTE-X19 where it was necessary.

3.2.P.5.4 Batch Analyses

A total of (b) (4) KTE-X19 clinical lots were manufactured for the ZUMA-2, ZUMA-3, and ZUMA-4 studies at (b) (4) and released with a target dose of (b) (4) CAR^+ T cells/kg and 2.0×10^6 CAR^+ T cells/kg. Out of (b) (4) lots, (b) (4) lots failed the appearance test in (b) (4) was manufactured and no product was released; for the remaining (b) (4) were manufactured - only (b) (4) from each of these lots failed appearance testing and the bag that passed appearance testing was released), (b) (4) lot failed (b) (4) (potency) testing and was released under FDA waiver, and (b) (4) lots did not meet target dose and were also released under FDA waivers. (b) (4) lot did not meet dose and released under physicians request and reported to respective Health Authority.

Reviewer comment: *Additional information regarding the (b) (4) lots that failed appearance testing was provided in Amendment #37 (response to CMC IR of 03APR2020) received 13APR2020. This information is acceptable.*

A total of (b) (4) KTE-X19 Process Performance Qualification (PPQ) lots were manufactured at full scale from healthy donor apheresis material (b) (4) donors) at (b) (4) to confirm the specification. Various parameters were validated, including (b) (4) intervention followed by (b) (4) at dose levels of (b) (4) 2×10^6 cells/kg. A summary of the batch analyses was provided and all PPQ lots met specifications (see Section 3.2.P.3.5.1 Manufacturing Process Validation and Table 84 for details). PPQ lot release testing results ranges are contained within the proposed specifications and are within the range of ZUMA-2 clinical lots for (b) (4), % cell viability, and (b) (4) (See Figure 40, Figure 41, and Figure 42). gentamicin and (b) (4) impurities were also assessed for the PPQ lots, but these impurities are not tested at lot release and specifications have therefore not been set for residual (b) (4) or gentamicin.



(b) (4)

3.2.P.5.5 Characterization of Impurities
Process and product-related impurities in KTE-X19 are described and reviewed in Section 3.2.S.3.2 Impurities.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:
The information provided in the batch analysis for PPQ and clinical lots is complete and acceptable. PPQ lot release testing results ranges are contained within the proposed specifications. Information regarding impurities is acceptable (see Section 3.2.S.3.2 Impurities (Kite Pharma, Inc., KTE-X19)) for details.

3.2.P.6 Reference Standards or Materials
This section reviewed by TS
The analytical methods for KTE-X19 produce quantitative results without requiring normalization to reference standards. Instead, KTE-X19 positive control test material (PCTM) is used in a number of release assays.

Positive Control Test Material (PCTM)

PCTM is used as a method-specific positive control in the following assays:

- Anti-CD19 CAR expression (i.e., (b) (4)
- (b) (4) for vector potency
- (b) (4) final product release
- (b) (4) for identity (b) (4)

PCTM is manufactured using the commercial KTE-X19 manufacturing process. It consists of (b) (4)

.

(b) (4)

Reviewer's Assessment:

The qualification acceptance criteria for (b) (4), which was a potential concern because a positive control would be expected to consistently (b) (4). In Amendment #14 (response to CMC IR of 31JAN2020) received 07FEB2020, it was confirmed that qualification of each PCTM lot uses (b) (4), each tested for (b) (4) For each (b) (4) must be positive for the lot to pass qualification. For final product (b) (4) replicates of the PCTM are tested and (b) (4) of these replicates must (b) (4) This is acceptable since (b) (4) is expected to (b) (4), providing additional assurance of assay validity. In addition, (b) (4) acceptance criteria for PCTM was initially set at (b) (4). This specification was revised in Amendment #31 (response to CMC IR of 13MAR2020) received 23MAR2020, to the range (b) (4), to reflect the fact that a positive control should actually be transduced.

The acceptance criteria for a positive control lot should ideally be tighter (i.e., in the positive direction) than the final product acceptance criteria to assure consistent positive results. However, the Agency recognizes that it would be difficult to identify PCTM lots meeting this standard for all assays. Kite stated that it is not required that a PCTM lot be qualified as an assay control for every assay, meaning that different PCTM lots could be designated as positive controls for different assays. This will make it easier to identify lots with relatively high-performance ranges for different assays. The current PCTM qualification protocol is acceptable as performance ranges are qualified using multiple vials, multiple analysts, and multiple laboratories according to validated methods. Moreover, the performance range is almost always narrower than the final product release specifications. In Amendment #24 (response to CMC IR of 28FEB2020) received 09MAR2020, it was confirmed that PCTM

results in release assays must be within the qualified performance range otherwise the assay is invalid. The PCTM qualification and its use as a control strategy in release assays is acceptable.

3.2.P.7 Container Closure System

This section reviewed by GEP

The primary container closure systems for KTE-X19 DP are commercially-available, (b) (4) ; Figure 43 and Table 102) and (b) (4) Figure 44 and Table 102) 510(k) cleared (b) (4) bags designed for storage of blood and blood products. These bags are also used for (b) (4) storage of (b) (4) manufactured by the same supplier was used in stability studies (see section 3.2.P.8).

Reviewer comment: *The same bags are used as DP container closures for YESCARTA®.*

In addition to these containers used in the (b) (4) filling process, a custom bag set (b) (4) kit (Figure 45) manufactured by (b) (4) filling process.

Reviewer comment: *Additional information regarding the (b) (4) kit was provided in Amendment #16 (response to CMC IR of 07FEB2020), received 14FEB2020. This information is acceptable.*

(b) (4)

(b) (4)

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

(b) (4)

Reviewer comment: *This data is provided in section 3.2.P.2.4 of the BLA, but is presented here for ease of review. It is identical to data provided and found acceptable in BLA 125643 Amendment #216 to support the use of* (b) (4) *bag types as primary container closures for YESCARTA®. As YESCARTA® and KTE-X19 are similar products that are formulated identically, this data is applicable to both products. There are no concerns regarding the effect of* (b) (4) *bags on product recovery,* (b) (4) *(potency), or fold-expansion. Note that while no specific studies were performed for the* (b) (4) *kit, the* (b) (4) *bags that comprise the final product container closure in this kit are identical to those used for manual filling.*

Extractables studies (Table 105) were performed on (b) (4) bags with and without labels and (b) (4) bags with labels using a (b) (4) as these may cause analytical challenges and assay interference.

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- **Secondary packaging (aluminum cryocassette)**

Once filled and sealed, each (b) (4) cryobag is placed into an aluminum cassette (Table 108) to provide protection during storage, shipment, and handling. Two different foam inserts to protect (b) (4) bags inside the aluminum cassette are used. Schematic diagrams of the cassette and inserts are provided and acceptable.

(b) (4)

(b) (4)

Reviewer assessment: *The aluminum cryocassette is identical to that used for YESCARTA® (reviewed in BLA 125643 OS), and is intended only to protect the product bags. The cassette will not directly contact the product at any time. Information regarding the foam inserts was provided in Amendment #19 (response to CMC IR of 14FEB2020) received 24FEB2020 and is acceptable. The proposed secondary packaging is therefore acceptable.*

- **Vapor phase liquid nitrogen shipper**

KTE-X19 packaged inside the aluminum cryocassette is shipped in a vapor phase liquid nitrogen shipper, described in Table 109 and Figure 46.

(b) (4)

The final product packaging has been demonstrated to adequately protect the product and maintain a temperature of ≤ -150°C during transportation (see Section 3.2.P.3.5.2.).

(b) (4)

(b) (4)

Reviewer comment: *Information regarding shipper charging and pack out, including SOPs 00628 (Packing and shipping final product) and 00638 ((b) (4)), was provided in Amendment #19 (response to CMC IR of 14FEB2020) received 24FEB2020 and is acceptable.*

Overall Reviewer's Assessment of Section 3.2.P.7:
Container closure and shipper information is acceptable. All information is similar to that previously reviewed for YESCARTA®, except for the (b) (4) bag kit which is new to this application. Information to clarify minor details was requested during the review cycle and responses were acceptable, as outlined above. There are no other concerns or outstanding deficiencies regarding container closures.

3.2.P.8 Stability

This section reviewed by GEP

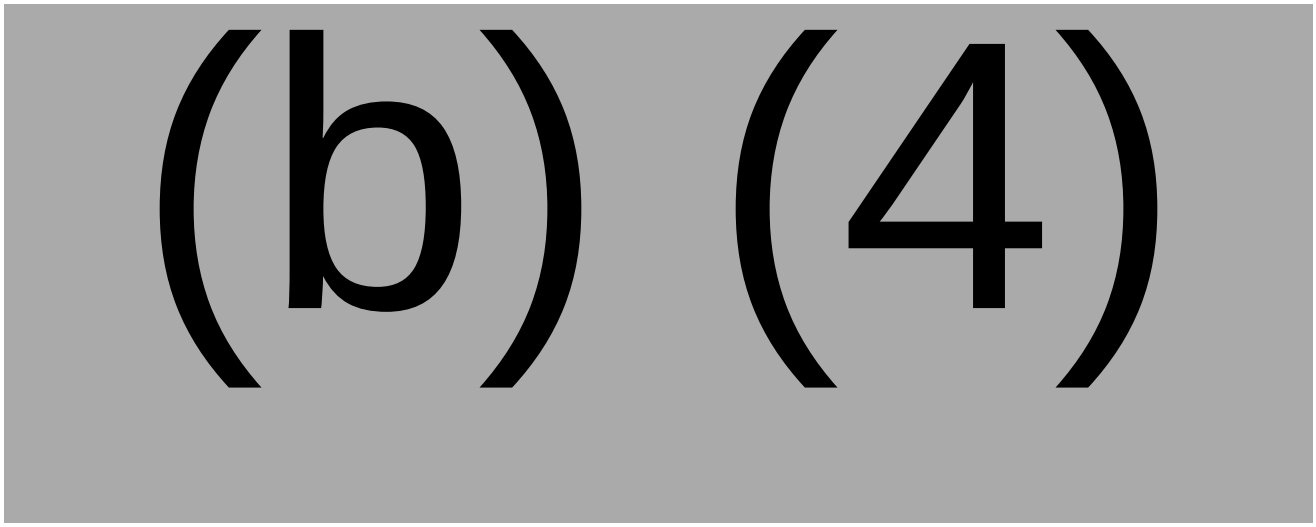
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The proposed shelf life of KTE-X19 is 12 months when stored at ≤ -150°C. Long term stability studies at ≤ -150°C to support the proposed shelf life have been completed for patient lots stored in the commercial container closure and healthy donor lots stored in smaller (b) (4) bags; studies on healthy donor PPQ and post-PPQ lots in the commercial container closure are ongoing. Accelerated and stress stability studies using heathy donor lots stored at (b) (4) , respectively have been completed. In use stability studies assessing thawed material held at room temperature have also been completed.

Long term stability studies

- **Clinical lots**

The most relevant material for stability studies to support product shelf life are KTE-X19 patient lots used in the clinical trials. However, the availability of this material is limited to 1 (b) (4) bags for patients who have dropped out of the clinical trials, or who died prior to product administration. A total of (b) (4) lots, all manufactured from (b) (4) material and (b) (4) filled into (b) (4) bags, were available for stability studies (b) (4) formulated at (b) (4) and (b) (4) formulated at 2.0×10^6 cells/kg), including (b) (4) lots that were returned from clinical sites. These were tested at lot release, and at either 12 (b) (4) months as outlined in Table 110.



Reviewer comment: *In Amendment #19 (response to CMC IR of 14FEB2020), received 24FEB2020, applicant clarifies that 9/10 clinical stability lots were manufactured at* (b) (4)*, rather than the* (b) (4) *commercial manufacturing site. Comparability between* (b) (4) *and* (b) (4) *has been demonstrated under BB-IND-16675 amendment #116 (see Section 3.2.S.2.6 Manufacturing Process Development). Note that lots were formulated at both* (b) (4) *2×10^6 cells/kg; as described under Section 3.2.P.3.5.1 Manufacturing Process Validation, both dose levels are relevant for assessing stability of KTE-X19.*

These patient lots were thawed and tested at the described time points with stability protocol acceptance criteria shown in Table 111; commercial acceptance criteria are shown for comparison.

Table 111. Acceptance criteria for long term stability studies using patient lots

Stability test	Test method	Protocol acceptance criteria	Commercial acceptance criteria
Product appearance	Visual inspection	(b) (4)	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles
Container appearance	Visual inspection	(b) (4)	N/A
Viability	(b) (4)	(b) (4)	(b) (4)
Anti-CD19 CAR expression	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	No growth	No growth

All lots met their acceptance criteria for product appearance, however one lot (b) (4) had a cracked bag at the (b) (4) month time point. Investigation did not reveal any laboratory or handling errors for this bag. The cracked bag was not tested for sterility, but sterility was maintained for all other lots. Viability, (b) (4), and potency results are shown in Figure 47.

Reviewer comment: *Additional information regarding cracked bags was provided in Amendment #19 (response to CMC IR of 14FEB2020) received 24FEB2020.* (b) (4)

This response is acceptable.

(b) (4)

(b) (4)

Reviewer comment: *A change in the* (b) (4) *method for assessing anti-CD19 CAR expression was introduced while these lots were on stability studies, such that all lots (except* (b) (4) *which were tested with* (b) (4) *using the new method at all timepoints) were tested with* (b) (4) *by the old method at lot release and by the new method at subsequent time points, as described in Amendment #31*

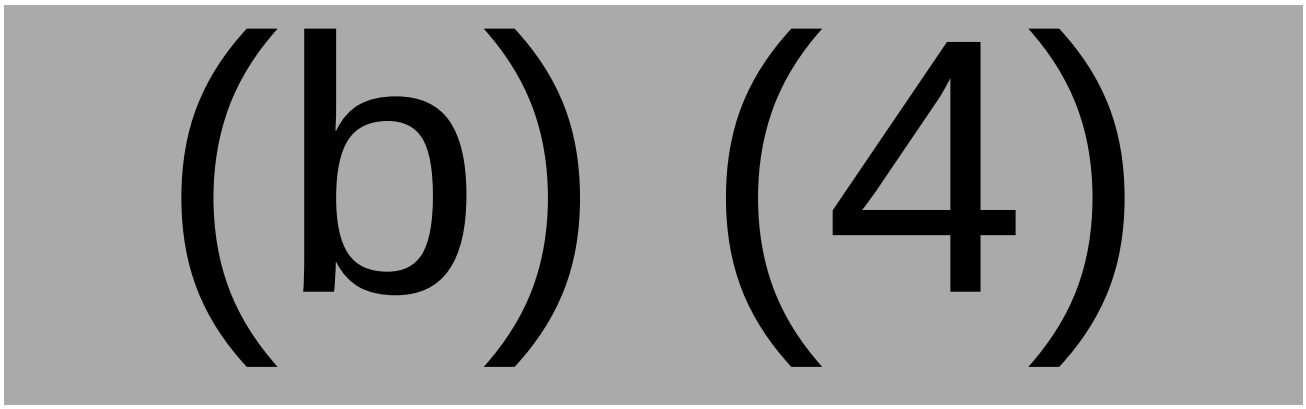
(response to CMC IR of 13MAR2020), received 23MAR2020. This is discussed in more detail below.

No root cause was identified for the lot that dropped below the protocol acceptance criterion, but this lot grew more slowly than normal and was manufactured from a second apheresis collected from the same patient, which might suggest a problem specific to that patient. In terms of potency (as assessed by (b) (4)), all lots meet the stability protocol acceptance criterion but (b) (4) filled at (b) (4) dropped below the proposed commercial acceptance criterion at (b) (4) months (an overall drop of (b) (4) relative to lot release value). A second lot filled at (b) (4) cells/kg dropped by (b) (4) at 12 months, but remained above commercial and stability protocol acceptance criteria. The applicant's conclusion is that clinical subject lots remain viable and potent for at least (b) (4) months at the recommended storage conditions of ≤ -150°C.

Reviewer assessment: *There are no issues with viability after long term storage, but the apparent decreases in (b) (4) and potency in some lots are potential concerns. The largest decreases in these parameters were seen in lots filled at (b) (4) with lesser decreases seen in lots filled at 2.0×10^6 cells/kg. However, only (b) (4) lots at the 2.0×10^6 cells/kg dose (which is the commercial dose level and thus most relevant for assessment of commercial product) were available for stability testing. As stability was assessed against a (b) (4) value and only a single time point could be assessed for each lot, it cannot be determined from this data whether the decreased (b) (4) and potency reflect one time drops on freeze/thaw or indicate a downward trend over time (or for (b) (4) reflect methodological changes). The fact that all clinical lots met all release criteria (save for the one lot that failed (b) (4) at 12 months) tends to support the applicant's (b) (4) month conclusion that lots are stable for (b) (4) months. However, the caveats stated above make this a tentative rather than definitive conclusion.*

- **Healthy donor lots filled at small scale**

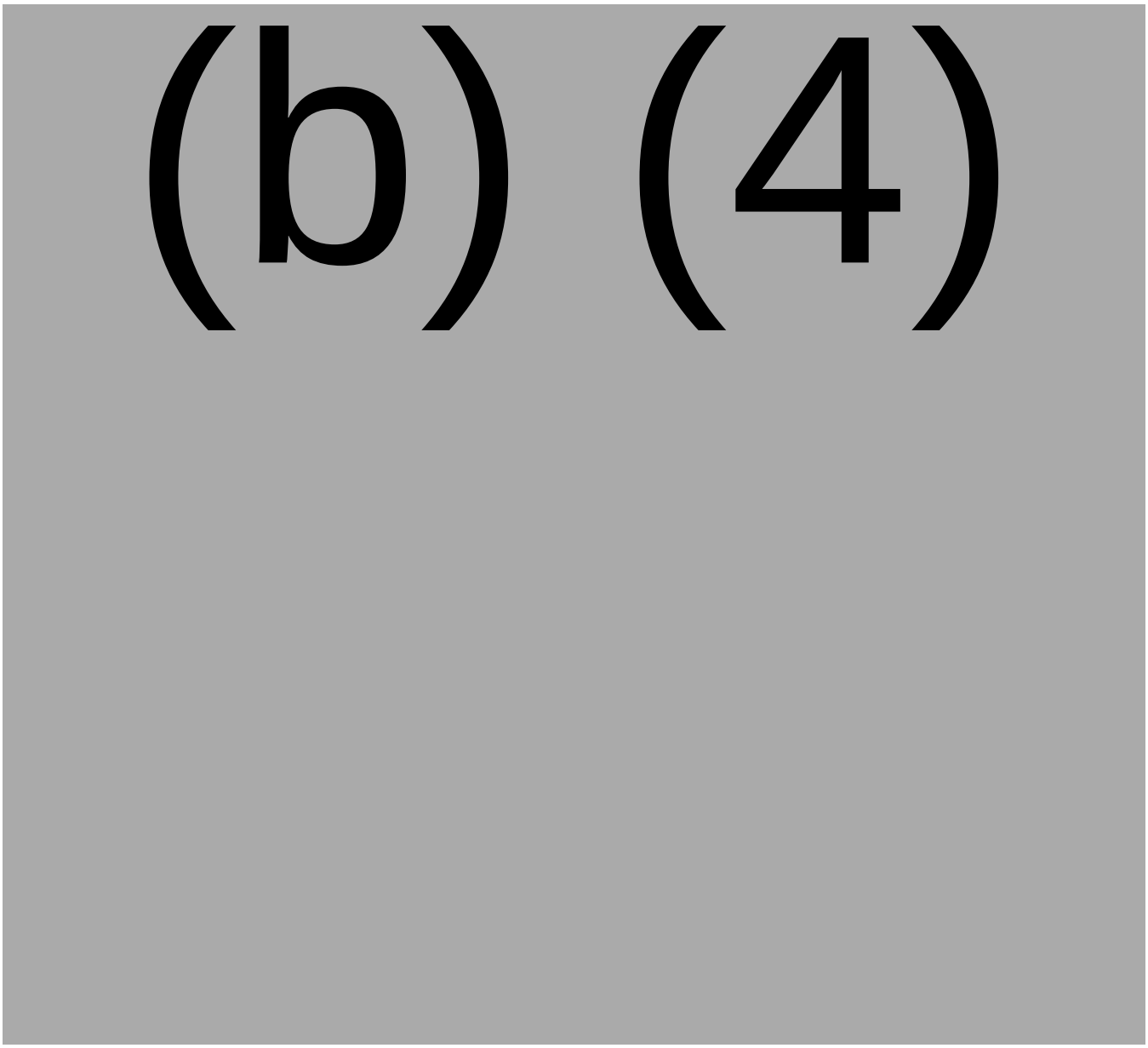
Stability of healthy donor lots was also assessed. Note that while use of healthy donor material allows more timepoints to be assessed (as no bags are required to treat patients), a possible caveat is that lots derived from healthy donors may not be fully representative of patient-derived lots. However, practical concerns make the use of healthy donor lots a necessity for stability studies of autologous products.Seven healthy donor lots manufactured from either (b) (4) enriched T cells were filled into multiple (b) (4) bags (b) (4) lots formulated at the (b) (4) level and (b) (4) at the 2.0×10^6 cells/kg level) as shown in Table 112.



Reviewer comment: *Use of multiple product aliquots in smaller bags enables testing at multiple time points. 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 and product cryopreservation attributes. This approach was also used for YESCARTA® (BLA 125643) and found acceptable. While stability testing using the same container closure as that for commercial distribution is required per cGMP regulations [21CFR 611.166(4)], clinical subject material and PPQ lots filled into the commercial container closure have also been studied for stability. In Amendment #19 (response to CMC IR of 14FEB2020) received 24FEB2020, applicant clarifies at which site each lot was manufactured* (b) (4) *and that time 0 corresponds to KTE-X19 product cryopreserved at ≤ -150°C for* (b) (4) *. This is acceptable.*

Stability acceptance criteria for healthy donor lots stored in (b) (4) bags were similar to those for clinical subject lots (Table 111), except for potency (b) (4) and anti-CD19 CAR expression (report results). (b) (4) T cell (b) (4) were also assessed in some early studies, but were discontinued as product knowledge grew and these parameters were shown not to be stability indicating. Product appearance criteria were passed for all bags at all time points, except for lot (b) (4) where a plastic particle was observed in the bag thawed at the 6 month time point; this was assessed to be unrelated to time on stability. Container acceptance criteria were met for all bags, except for lot (b) (4) months, where the bag was found to be cracked; a second bag was thawed that met container acceptance testing criteria. No root cause was identified for this deviation. Sterility was assessed at lot release and (b) (4) months (except for the (b) (4) cracked bag) and met acceptance criteria.

Viability, (b) (4) , and potency results over time are shown in Figure 48.



Viability was maintained close to lot release levels out to 6 months in all cases, dropping somewhat for (b) (4) lots at 9 months onwards, but remaining above both protocol and commercial acceptance criteria in all cases. (b) (4) fluctuates but remains above both stability protocol and commercial acceptance criteria for all lots at all times. However, CAR expression remained similar to lot release levels for the (b) (4) lots manufactured at (b) (4) out to 6 months, but then apparently dropped (b) (4) from lot release levels and remained steady thereafter. CAR expression drops slightly from (b) (4) levels at the initial post-thaw timepoint for the (b) (4) lots manufactured a (b) (4), fluctuating thereafter for these lots. From the data, lots manufactured at (b) (4) are clearly stable out to (b) (4) months.

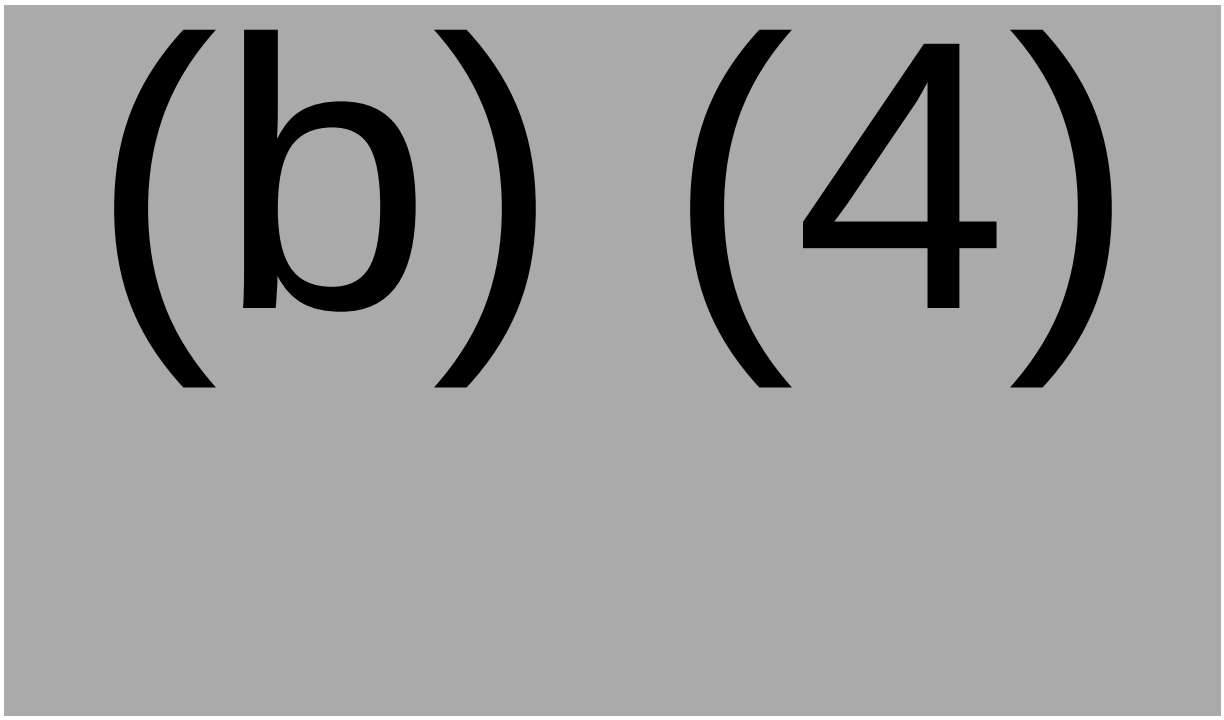
Reviewer comment: *The % CAR expression data showed a substantial decrease (b) (4) between 6 and 9 months for the (b) (4) lots manufactured at (b) (4) (but not for the (b) (4) lots manufactured at (b) (4). This lower % CAR expression was then maintained through the remainder of the study (out to (b) (4) months). In Amendments #24 and #31 (responses to CMC*

IRs submitted 28FEB2020 and 13MAR2020, respectively), this was explained by the applicant as being due to a change in the method used to (b) (4) *from using PCTM to using a* (b) (4) *This change was introduced in MAR2018, such that the stability lots manufactured at* (b) (4) *were tested using* (b) (4) *by the new method from the 9 month timepoint onward. Lots manufactured and tested at* (b) (4) *were not subject to this until the* (b) (4) *month timepoint, due to a slower rate of reagent consumption at this facility. All timepoints for PPQ stability lots, accelerated stability lots, and stress stability lots were tested subsequent to this change, and are thus unaffected by it.*

This method change complicates assessment of healthy donor lot stability in terms of CAR expression. In terms of potency, (b) (4) *levels fluctuate over time for lots produced at both sites; at 12 months levels are on average* (b) (4) *of lot release values (95% CI* (b) (4) *N=*(b) (4) *and at* (b) (4) *months on average* (b) (4) *(95% CI* (b) (4) *N=*(b) (4)*. Conclusions are difficult to draw for this parameter due to the wide confidence intervals. However, all stability parameters remained above lot release criteria for all healthy donor lots at all timepoints. Overall, despite the issues noted above, this healthy donor data tends to support the proposed shelf-life for KTE-X19 of 12 months (and in fact support* (b) (4) *months), with the caveat that these* (b) (4) *lots were filled into small-scale container closures (lots filled into commercial container closures are more reflective of the commercial product). Thus, as with the clinical lots, this should be regarded as supportive rather than definitive data.*

- **PPQ (healthy donor) lots filled into the commercial container closure system**

Additional stability studies using (b) (4) healthy donor-derived KTE-X19 PPQ lots and (b) (4) post-PPQ lots (described in Table 113) all manufactured at (b) (4) and stored at ≤ -150°C are in progress.



(b) (4)

Reviewer comment: *The stability testing schedule for PPQ lots was revised as described in Amendment #31 (response to CMC IR of 13MAR2020) received 23 MAR2020. This change was due to an investigation into non-reportable* (b) (4) *results at the 3 month time point; this issue was resolved and resulted in previously planned assessments at 6 months being shifted to 9 months. This is acceptable.*

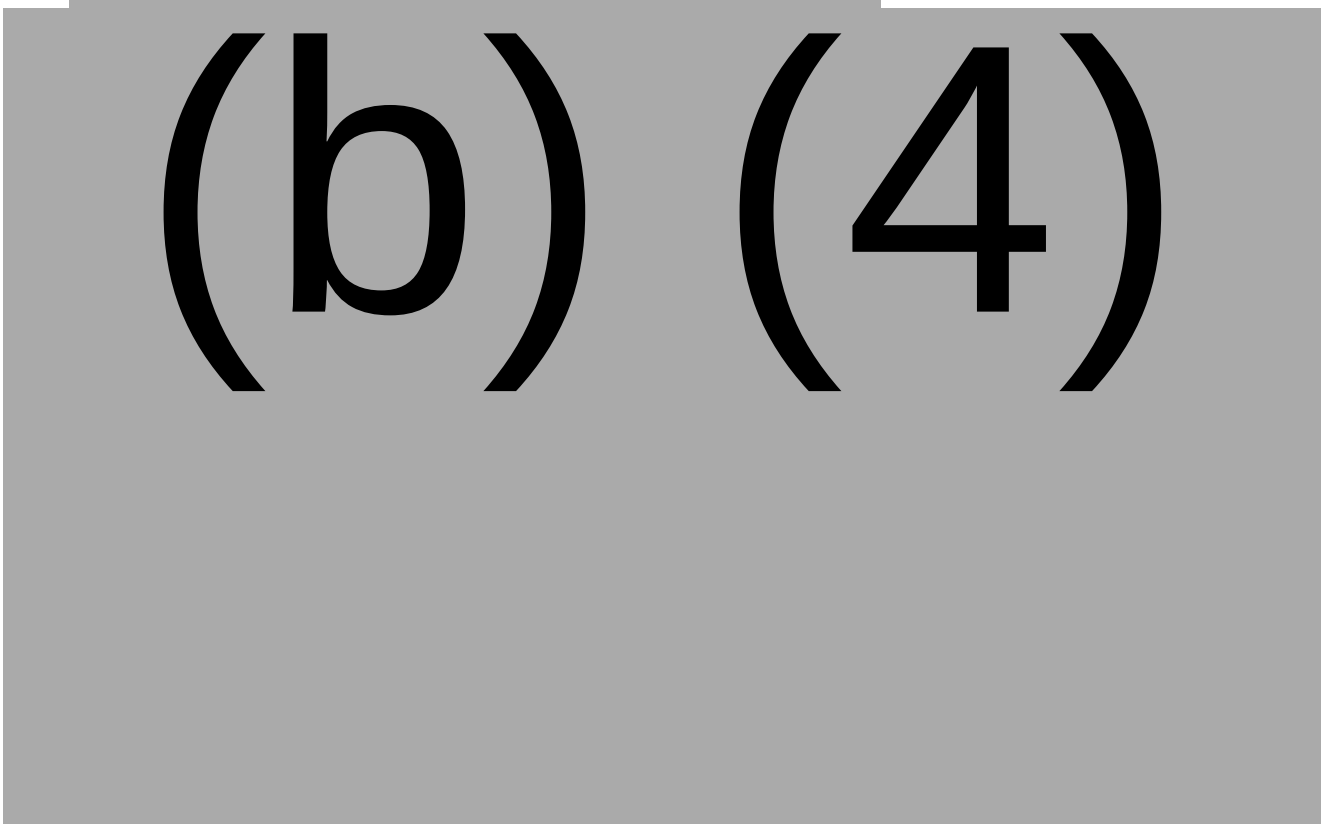
Acceptance criteria for PPQ stability lots are the same as for clinical lots (shown in Table 111). Viability, % CAR expression, and (b) (4) results are shown in Figure 49.

(b) (4)

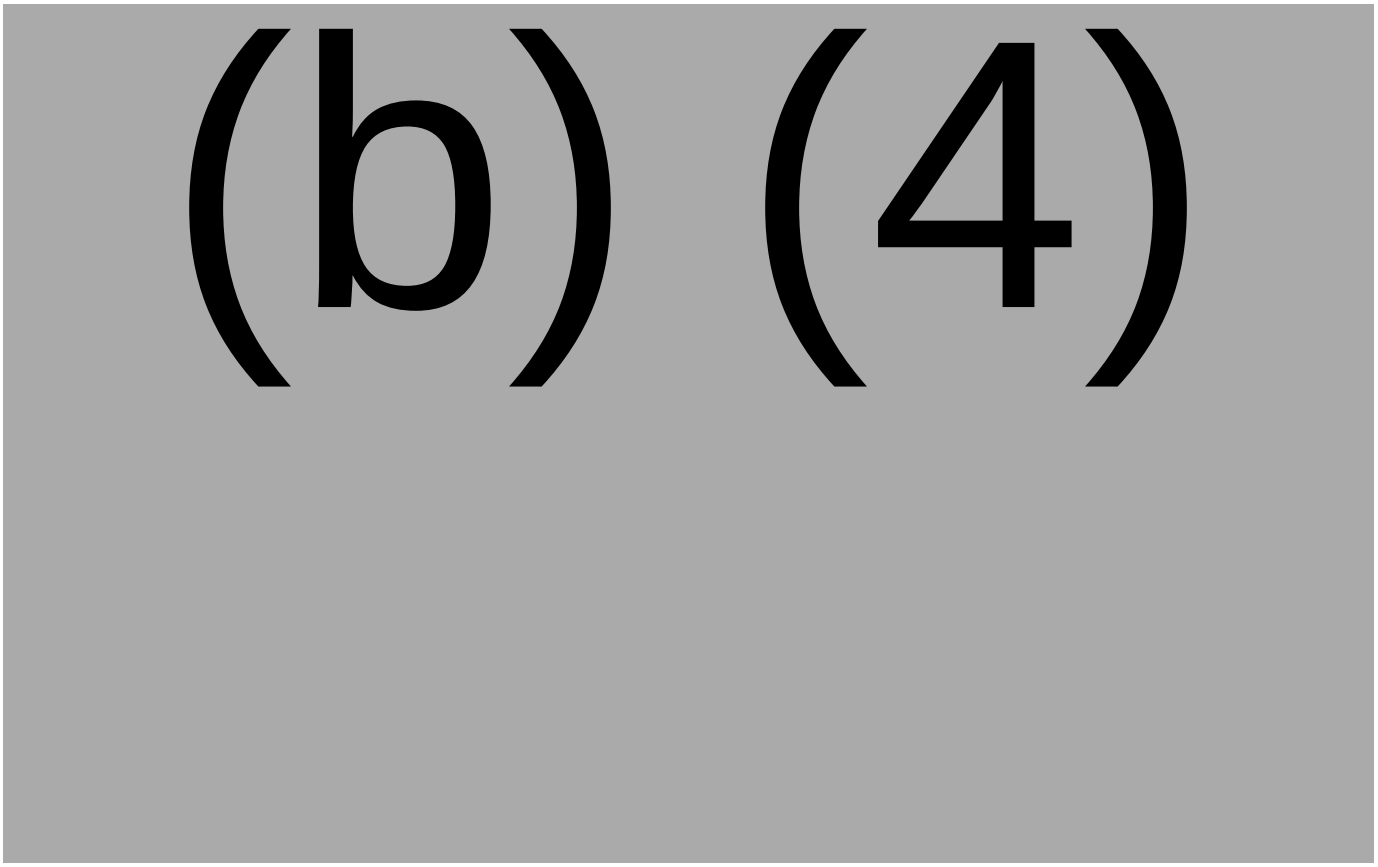
(b) (4)

Viability results are shown in Figure 49. Analysis of covariance (ANCOVA: factor = lot; dependent variable = $\log_{10}$ viability; covariant = time) indicated that viability data from individual lots is not poolable, thus data was assessed by repeated measures analysis of variance (RM ANOVA), which revealed that there was no significant difference in viability between different time points. In (b) (4) cases, there was a small (b) (4) drop in viability between lot release and 3 months, but this recovered back to baseline at 12 months. All lots remained above the viability release specification at all time points.

(b) (4)



Anti-CD19 CAR expression results are shown in Figure 50. ANCOVA (factor = lot; dependent variable = $\log_{10}$ CAR expression; covariant = time) showed that slopes from individual lots are not poolable. RM ANOVA analysis indicated that % CAR expression was significantly different (P <0.05) from lot release at all subsequent time points. However, from visual examination of the data, it appears that there is an relatively large initial drop in % CAR expression between the (b) (4)) lot release value and the first assessed time point (i.e., 3 or 9 months) but a much smaller change between the first and second time points (i.e., 3 vs. 12 months). Thus, losses in CAR expression may be more related to the freeze/thaw process rather than to length of time in storage. Regardless, all PPQ lots met the commercial acceptance criteria for % CAR expression at all stability time points out to 12 months.



Potency (b) (4)) results are shown in Figure 51. Note that (b) (4) results at the (b) (4) month time point from (b) (4) lots were not reportable due to an invalid assay; investigation of this issue caused the planned 6 month time point to be shifted to 9 months. Regression analysis by 1-sided ANCOVA (factor = lot; dependent variable = $\log_{10}$ (b) (4) covariate = time) showed no significant variation (*P* = 1.00) between the factor and covariate, passing the assumption that slopes for each lot are equal. ANCOVA also indicated that there was no significant difference in the intercepts (P = (b) (4), allowing the slopes to be pooled for analysis. The resulting exponential decay regression line showed no overall trend toward loss of potency over 12 months. However, as assessed by RM ANOVA potency for all lots tested dropped significantly (*P* = (b) (4) from lot release (b) (4) levels at 3 months, but recovered at 9 and 12 months (b) (4) values). One lot (b) (4) dropped below the commercial acceptance criterion at 3 months (result (b) (4) vs. specification of (b) (4) but rebounded at 12 months. All other lots met commercial acceptance criteria at all time points tested.

Reviewer comment: *Additional stability data from PPQ lots out to 9 months was provided in Amendment #19 (response to CMC IR of 14FEB2020) received 24FEB2020, and data to including the 12 month time point was provided in Amendment #46, received 18MAY2020. PPQ lot stability data is likely the most reflective of the commercial product, as PPQ lots were manufactured at* (b) (4) *using the final commercial process and were filled in to the full scale commercial container/closure system using* (b) (4) *methods. The PPQ lot stability data supports a 12 month shelf life for KTE-X19. It is possible that this may be extended based on future* (b) (4) *) results from ongoing PPQ stability studies.*

- **In-use stability studies**

KTE-X19 is to be administered by intravenous infusion, to begin within 30 minutes after thawing with a target infusion time of 30 minutes. To assess post-thaw stability and the effect of potential delays between thawing and infusion, two sets of in-use stability studies were performed where healthy donor-derived lots filled into (b) (4) bags were cryopreserved for various lengths of time prior to thawing and holding at room temperature for 3 hours, as shown in Table 114. Test methods and acceptance criteria are shown in Table 115.

Table 114. KTE-X19 lots tested for in-use stability studies

Study	Lot number	Time stored at ≤ -150°C	Time points tested
1	(b) (4)	6 weeks	Immediately post thaw, and after 3 hours at room temperature
		6 weeks	
		6 weeks	
2		6, 12, (b) (4) months	Immediately post thaw, and after 3 hours at room temperature
		6, 12, months	
		6, 12, months	

Table 115. Acceptance criteria for in-use stability studies

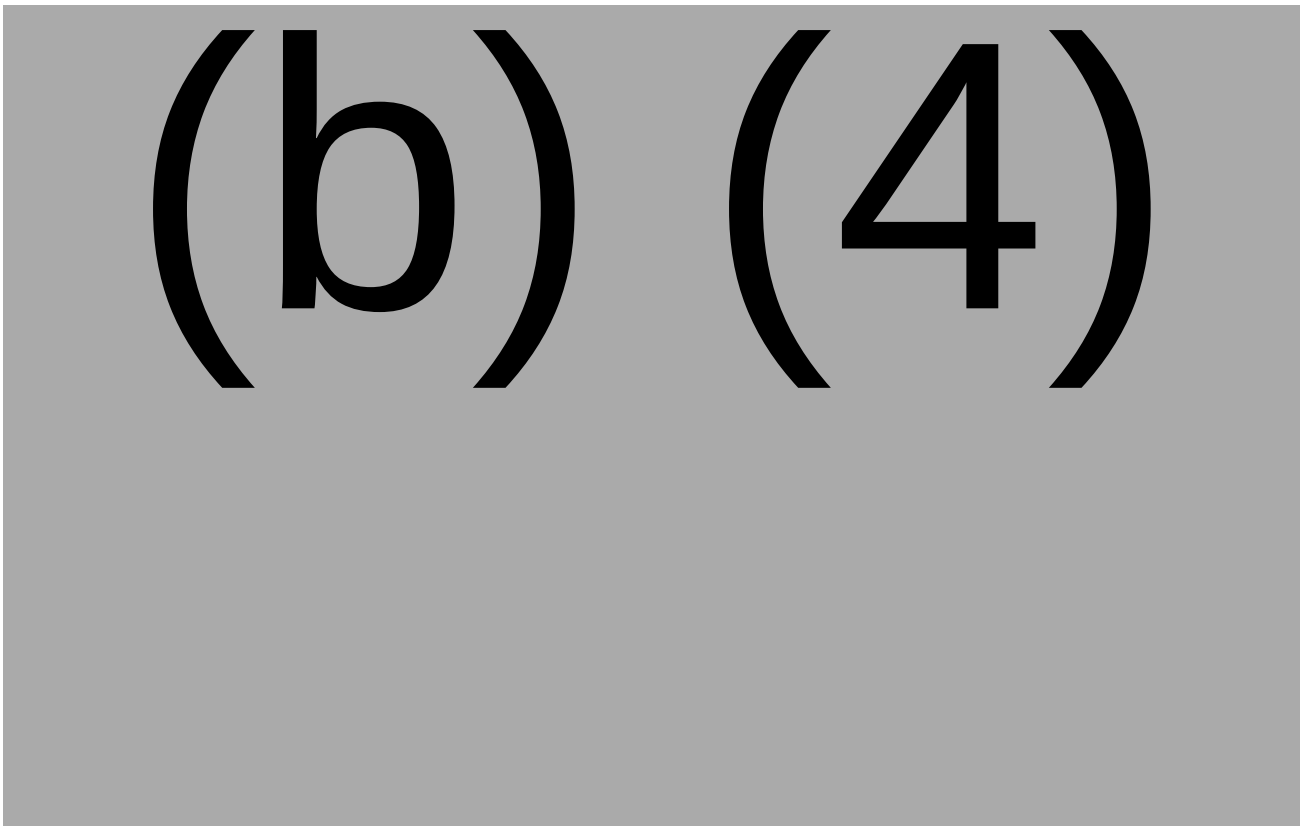
Test method	Study 1 acceptance criteria	Study 2 acceptance criteria	Commercial acceptance criteria
Cell count	(b) (4)		
Anti-CD19 CAR expression			
Potency by (b) (4) (b) (4)			
T cell (b) (4)			
(b) (4) (b) (4)			

In the first study, viable cell count, % recovery and CAR expression remained stable (b) (4) between immediately after thawing and after 3 hours at room temperature. For each time point tested in the second study, all parameters met protocol acceptance criteria (and commercial acceptance criteria) both immediately after thaw and 3 hours at room temperature. Viability and CAR expression changed by (b) (4) over the 3 hour period, while (b) (4) was slightly more variable (likely reflecting assay variability). T cell (b) (4) changed little over 3 hours.

Reviewer assessment: *The KTE-X19 lots used for these in-use stability studies were healthy donor-derived and filled into (b) (4) bags rather than being patient-derived material filled into the commercial container-closure. In Amendment #19 (response to the CMC IR of 14FEB2020) received 21FEB2020, the applicant confirmed that no in use stability studies were performed with lots filled into the commercial container closure, providing the justification that final product filled into (b) (4) bags has been demonstrated to be comparable to lots filled into the commercial container closures as described in Section 3.2.P.2.3.2.2 of the BLA. This bag comparability information is identical to that previously reviewed and found acceptable for YESCARTA® (BLA 125643). Overall, these in use stability studies demonstrate that KTE-X19 is stable at room temperature for 3 hours post thaw.*

- **Accelerated stability studies**

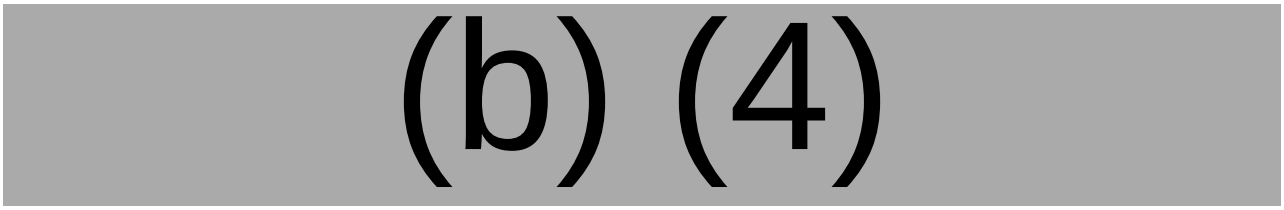
Accelerated stability studies of KTE-X19 held at (b) (4) were conducted over 3 months using (b) (4) healthy donor lots manufactured in April 2019 at (b) (4), each filled into full size (b) (4) bags at (b) (4) cells/dose. Accelerated stability data is shown in Table 116.



Reviewer comment: *Revised accelerated stability data (including raw viable cell counts and lot release values) was provided in Amendment #31 (response to CMC IR of 13MAR2020) received 23MAR2020. This data is acceptable; however, it should be noted that over time at (b) (4) there was a marked downward trend in potency (b) (4) compared to lot release values. This was not reflected in CAR expression, cell count, or viability. Despite this trend for (b) (4), both lots met protocol acceptance and lot release criteria for all parameters out to (b) (4) months of storage at (b) (4).*

- **Stress stability studies**

(b) (4) KTE-X19 (lot # (b) (4) was manufactured in May 2019 at (b) (4) from healthy donor apheresis material, filled at a dose level of (b) (4) cells/kg into small-scale (b) (4) bags, stored at (b) (4) for up to (b) (4), and tested as shown in Table 117.



(b) (4)

(b) (4)

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

Kite Pharma commits to continue the long term stability studies that have already been initiated, and commits to extend the expiry period only after satisfactory stability data have been obtained and with appropriate regulatory notification. In addition, (b) (4) one healthy donor lot of KTE-X19 will be manufactured and filled into (b) (4) bags. This lot will be tested for stability per the protocol described in Table 118 and results will be evaluated against the commercial specifications described in Table 93 (Section 3.2.P.5.1).

Table 118. Post-approval long term stability testing protocol (≤ -150°C)

Test	Time points (months						
	LR[1]	0[2]	3	6	12	(b) (4)	(b) (4)
Container appearance	X	X	X	X	X	X	X
Cell viability	X	X	X	X	X	X	X
Anti-CD19 CAR expression	X	X	X	X	X	X	X
Potency by (b) (4)	X	X	X	X	X	X	X

[1] Results obtained from (b) (4)

[2] Results obtained from testing after cells have been cryopreserved at ≤ -150°C

A separate stability program will be performed to confirm that full scale cryostorage bags used for commercial product provide suitable protection from microbial contamination. (b) (4) lot of KTE-X19 will be produced (b) (4) and filled into a commercial container closure selected from one of the two options (b) (4) bags). For these studies, product and container appearance will be monitored and sterility testing will be performed at the end of the expiration period.

Reviewer comment: *Similar maintenance of sterility studies are performed for YESCARTA®. This is acceptable.*

Overall Reviewer's Assessment of Section 3.2.P.8:
The proposed shelf-life for commercial lots of KTE-X19 is 12 months at ≤ -150°C. Long-term stability studies to support this are summarized as follows: Clinical (patient) lots stored in the commercial container closure system generally were generally stable out to (b) (4) months; caveats are that only (b) (4) lots in total were tested at either 12 (b) (4) (b) (4) months. Healthy donor lots met all lot release criteria out to (b) (4) months, however a limited number (b) (4) of lots were assessed (b) (4) manufactured at (b) (4) and were filled into a small-scale container closure system (b) (4) bags) instead of the commercial container closure. Analysis of clinical and healthy donor lots is further complicated by a method change affecting the CAR expression (b) (4) assay. Data from (b) (4) healthy donor-derived PPQ lots is still being collected (planned study duration is (b) (4) months). All data points so far (with one exception for (b) (4) meet commercial acceptance criteria out to 12 months. Importantly, these PPQ lots were all manufactured at the commercial production site (b) (4) , were filled into the commercial container closure, and are unaffected by assay method changes; data from PPQ lots is therefore likely to be the highest quality available. PPQ lots currently support a 12 month shelf life. Based on the totality of the long term stability data, the shelf life for KTE-X19 should be set at 12 months from the date of cryopreservationat ≤ -150°C. This was communicated to the applicant on 11JUN2020, and confirmed in amendment #49 received 19JUN2020.

In use stability testing supports a post-thaw expiry of ≤ 3 hours. Accelerated and stress stability studies are acceptable and demonstrate that (as with YESCARTA®) (b) (4) production is a stability-indicating parameter for KTE-X19.

The post-approval stability protocol, including maintenance of sterility studies, is acceptable.

Clarifications and additional data were requested for Section 3.2.P.8 during the review cycle, as outlined above. All information requests were addressed and responses were acceptable.

3.2.A APPENDICES

This section reviewed by GEP

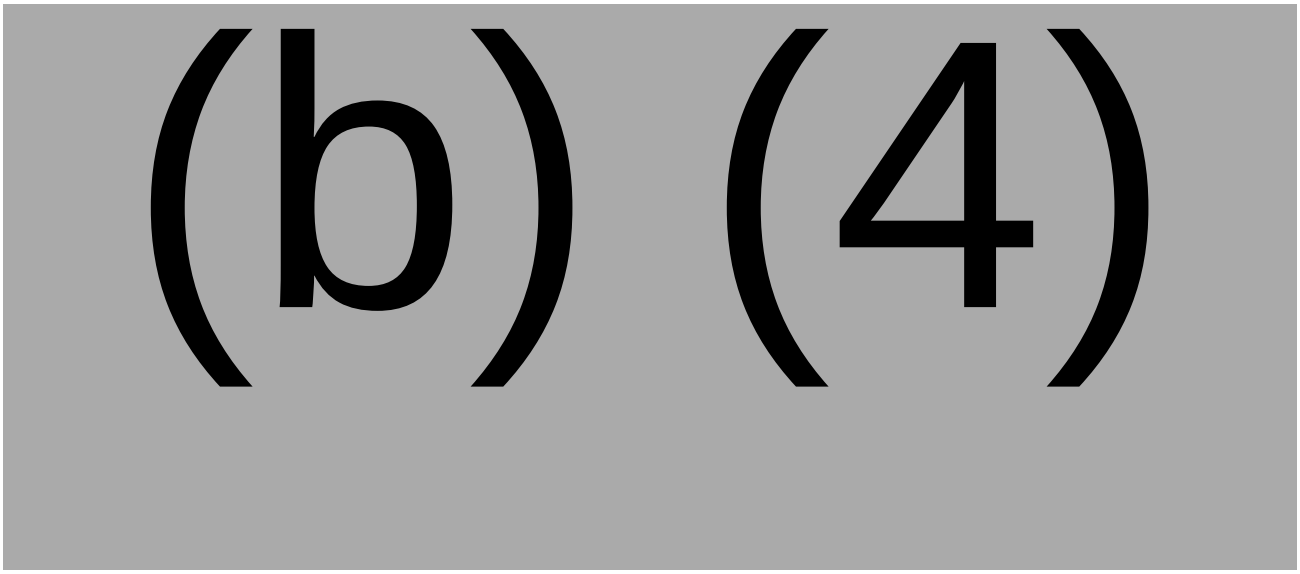
3.2.A.1 Facilities and Equipment

Two facilities are used for manufacture of KTE-X19:

(b) (4) is the manufacturing site for the (b) (4) vector used in both YESCARTA® and KTE-X19. Detailed information for this facility, equipment, and quality systems is provided in the Type V Master File (BB-MF-(b) (4)). Aseptic process validation (APV) for vector manufacture, including process simulation runs, has been completed at (b) (4)

The Kite Pharma (b) (4) facility is the manufacturing and release testing site for KTE-X19. (b) (4) is also the site for YESCARTA® manufacture. In summary, (b) (4) contains (b) (4) ISO (b) (4) manufacturing suites, and an ISO (b) (4) Media Prep room. The ISO (b) (4) suites have unidirectional gowning/degowning rooms, unidirectional pass throughs, and an independent HEPA-filtered HVAC unit to maintain correct pressure differentials. Support areas including corridors and a kitting room are ISO (b) (4) The facility also includes QC laboratory space and equipment required for in-process, lot release, and stability testing, and warehouse space for receipt and storage of raw materials (including apheresis material). Product storage (LN_2 freezers) and shipping preparation (pack out) facilities are also included.

Between them, the ISO (b) (4) suites contain a total of (b) (4) workstations; each workstation includes an ISO (b) (4) BSC and associated equipment for cell processing (e.g., (b) (4) , incubator, etc.). All product-contact surfaces are (b) (4) consumables that are provided sterile and ready to use. APV for the facility, equipment and KTE-X19 process has been completed. Ongoing aseptic operation qualification (AOQ) and an annual requalification program (with media simulations) has been established. Manufacturing equipment is listed in Table 119.



Reviewer comment: *A comparison of equipment used in the manufacturing processes for KTE-X19 and YESCARTA was provided in Amendment #8 (response to DMPQ IR of*

14JAN2020) received 22JAN2020. This information confirms that there are no differences in equipment except for the use of the (b) (4) *for the KTE-X19 process but not in the YESCARTA® process. There are also minor differences in* (b) (4) *consumables between the* (b) (4) *processes. This is acceptable.*

Descriptions of the (b) (4) *device and the* (b) (4) *, including installation, operation, programs, and performance qualification (including aseptic process studies) were provided in Amendment #27 (response to DMPQ IR of 26FEB2020) received 11MAR2020. The information provided is acceptable. Note that as described in Amendment #10 (response to DMPQ IR of 24JAN2020) received 29JAN2020, performance data for the* (b) (4) *master files (BB-MF-*(b) (4) *and BB-MF-*(b) (4) *respectively). These master files have been assessed by consult reviewers and found acceptable. There are no outstanding concerns.*

Only one product lot may be actively processed at each workstation at a given time, with required changeover procedures performed between lots to maintain segregation. The chain of identity/chain of custody (COI/COC) system is described in detail below, as this is critical for product tracking and control.

Reviewer comment: *The* (b) (4) *contract manufacturing facility and* (b) (4) *were reviewed by DMPQ (see DMPQ review for additional details). Both facilities were subject to pre-license inspection (PLI) for YESCARTA® (BLA 125643) in* (b) (4) *and* (b) (4) *inspection in* (b) (4) *. Therefore, PLI was waived for this BLA per CBER/OCBQ/DMPQ. However, since the 2017 PLI manufacturing operations have expanded to a total of* (b) (4) *an additional suite* (b) (4) *is fully constructed and will be made operational per product demand. In addition, the QC laboratory facilities have been expanded to support increased production volume. There are no outstanding concerns with these facilities.*

3.2.A.1.3. Chain of Identity/Chain of Custody (COI/COC)

To ensure that the correct cells are tracked from apheresis through the manufacturing process to infusion into the same patient, a chain of identity/chain of custody system has been developed with the terms defined as follows:

- Chain of Identity (COI) – the linkage of the patient to their apheresis material.
- Chain of Custody (COC) – the linkage of sequential events (via SOPs and electronic systems) that confirm COI at each movement and human transfer of the apheresis material through to final product

The COI is established via three unique and linked numbers (the Kite Patient ID, COI, and Cell Order number; see Table 120). These numbers are used to maintain the COC throughout the manufacturing process to product administration. COI is confirmed at each step by barcodes or human-readable numbers on the apheresis, in-process, and final product labels. COI numbers must match associated documentation as required by written procedures. Discrepancies are addressed when they occur, prior to proceeding to the next step. Each COI check generates a COC event that is recorded in the controlling electronic system or batch document to create the COC record. The COC record is reviewed as part of the product disposition process. COI/COC process steps throughout the whole manufacturing process (apheresis to are infusion) are outlined in Table 121.

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

(b) (4)

Reviewer comment: *Labeling of product bag and cassette was clarified in Amendment #24 (response to CMC IR of 28FEB2020) received 09MAR2020, such that the first set of labels (patient ID labels containing COI/COC information) are applied to the cassette and the corner of the final product bag (so as not to obscure the view of the product bag) once the product is formulated, and the second set of labels (product labels, containing product information) are applied to the cassette prior to visual inspection and to the front of the product bag after visual inspection. Retain copies of each label (Patient ID and Product label) are kept with the lot specific batch documentation. This is acceptable*.

Note that each bag of apheresis material is manufactured (b) (4)

(b) (4)

(b) (4)

Reviewer comment: *In Amendment #14 (response to CMC IR of 31JAN2020) received 07FEB2020, it was confirmed that KTE-X19 and YESCARTA® have unique final product item numbers integrated into the COI and COC. In addition, it was confirmed that there have been no instances of an incorrect product being manufactured at Kite (see Table 122).*

(b) (4)

Reviewer comment: *The KTE-X19 COI/COC system (already established and active for YESCARTA®) was originally designed to ensure the apheresis material and product can be*

tracked from "vein-to-vein" such that the correct patient receives their correct autologous (patient-specific) product. Because KTE-X19 and YESCARTA® have similar final product compositions (despite different manufacturing processes) and the same vector is used for manufacture of both, there is no product-specific identity test that distinguishes between these two anti-CD19 CAR T cell products. Therefore, the COI/COC system is crucial to ensure that the correct autologous product is administered, but also that this product has been manufactured via the correct process. After discussion with OCBQ, the combination of methods to maintain and control product identity (i.e., (b) (4) to identify (b) (4) and a validated COI/COC system to identify the patient-specific lot by physical means, including batch records and final product labels) is sufficient to meet the requirements of 21 CFR 610.14 (i.e., "The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests"). Note that in terms of risk, the key theoretical risk of manufacturing anti-CD19 CAR T cells via the wrong process (i.e., mistakenly using the YESCARTA® process instead of the KTE-X19 process) would be the possibility of transducing circulating MCL tumor cells that would not be removed by the YESCARTA® process; these cells would have to survive the culture process to be reinfused into the patient, where they could proliferate. This rare event has been documented for a different CD19 CAR T cell product, where the tumor cells lost cell surface CD19 expression due to intracellular sequestration of CD19 by the CAR transgene. A greater risk would be administration of the wrong patient's cells (by a break in COI/COC) which could result in graft vs. host disease. To date, COI/COC procedures have been effective at preventing this. In summary, the COI/COC system is acceptable for maintaining control of KTE-X19.

3.2.A.1.3.4 Apheresis center and treatment site qualification and monitoring
Apheresis site qualification
Apheresis sites are qualified based on successful completion of an onsite audit and completion of required onboarding activities. Audit elements include assessment of the apheresis facility areas (adequate size and control for receiving, preparation, collection, storage and shipping of apheresis material), equipment (makes/models used, calibration status, maintenance history), staff (staffing levels, training), FACT accreditation, documented site procedures for training, COI/COC, and handling of apheresis material. Once the audit certificate is issued, onboarding activities (completion of Kite Pharma training for receipt, handling, and control of apheresis shipper kits, proper labeling to ensure COI/COC, and use of the (b) (4) will be imitated. Once onboarding is completed, Kite Quality creates an entry for that site in the (b) (4) software; the site then becomes active and access is granted to (b) (4).

Treatment site qualification
Treatment sites are qualified based on successful completion of an onsite audit (assessing COI/COC procedures including correct transfer and handling of product and confirmation of patient identity and correct product at time of treatment, treatment site areas, staff training, and documented procedures), completion of onboarding activities (confirmation of training in final product receipt, handling, storage, tracking, thawing and hold times, COI/COC

procedures, identification and reporting of product complaints and adverse events), and completion of the REMS program requirements. Once these steps are completed, the treatment site is activated in the (b) (4) software.

Apheresis and treatment site monitoring
To ensure that they maintain qualified status, Kite Quality conducts regular monitoring of apheresis and treatment sites through a series of remote and onsite audits according to a defined schedule. Additional "for cause" monitoring may be conducted if there is a risk to product safety, and sites may be disqualified based on the results. Disqualified sites have their status changed in the (b) (4) system, preventing future orders from being placed and precluding scheduling of apheresis or treatment procedures at that site.
Reviewer comment: *These qualification procedures are the same as those established for YESCARTA® and are acceptable.*

Overall Reviewer's Assessment of Section 3.2.A.1:
The manufacturing facilities (b) (4) were not subject to pre-license inspection for this BLA due to a satisfactory recent inspectional history. Control and tracking of individual KTE-X19 products identity is established and maintained via a validated Chain of Identity/Chain of Custody (COI/COC) system, which (in combination with (b) (4) testing for the CAR transgene) is sufficient to ensure product identity. An acceptable qualification program for apheresis collection sites and treatment sites has been established, with an ongoing monitoring program. Minor issues were clarified through information requests during the review cycle, as outlined above. All responses were acceptable. There are no outstanding facility-related concerns.

3.2.A.2 Adventitious Agents Safety Evaluation
This section reviewed by GEP
3.2.A.2.1 Introduction and Summary
KTE-X19 is an autologous, gene-modified adoptive cellular immunotherapy, precluding use of traditional sterilization and virus clearance methods. To ensure product safety, procedural controls are followed for acceptance of materials used in manufacture of the (b) (4) vector and KTE-X19, 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 the (b) (4) vector
3. Sourcing of media and reagents used in KTE-X19 manufacture 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
(b) (4)

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

(b) (4)

3.2.A.2.3 Control of Adventitious Agents in the production of KTE-X19

Potential sources of adventitious agents that may be introduced during manufacture of KTE-X19 are outlined in Table 124, and include patient-derived apheresis material, the (b) (4) vector, and components of the culture and cryopreservation media (including reagents used in manufacture of these components).

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.A.2:
The measures for control of adventitious agents are acceptable as submitted. While the theoretical excess vector clearance of (b) (4) is borderline, the lack of detectable residual virus genome and infectivity in the final product provides additional reassurance that no vector will remain in the final product. There are no other concerns.

3.2.A.3 Novel Excipients
Not applicable. No new excipients are used in KTE-X19 manufacture.

3.2.R Regional Information (USA)

- **Executed Batch Records**

A blank Master Production Record (MPR) is provided. Executed batch records are provided as follows:

- (b) (4) Process: PPQ lot (b) (4) manufactured at (b) (4) in MAR2019
- (b) (4) Process: PPQ lot (b) (4) manufactured at (b) (4) in APR2019
- (b) (4) Reprocessing: PPQ lot (b) (4) manufactured at (b) (4) in MAY2019
- (b) (4) Recovery: PPQ lot (b) (4) 0 manufactured at (b) (4) in MAR2019

Reviewer comment: *The provided batch records are acceptable. There are no concerns.*

- **Method Validation Package**

Summaries of detailed method protocols and validation reports were provided in Sections 3.2.S.2.4 Controls of Critical Steps and Intermediates, and 3.2.P.5 Control of Drug Product. Method validation packages were reviewed and discussed in the relevant sections above.

- **Combination Products**

Not applicable. KTE-X19 is not a combination product.

- **Comparability Protocols**

No future manufacturing changes to be evaluated under a comparability protocol are proposed.

- **Additional Information in 3.2.R**

Section 3.2.R also contains clinical lot release testing results from the ZUMA-2 study, and a Microsoft Excel spreadsheet containing ZUMA-2 clinical lot release information with clinical and safety information.

Reviewer comment: *The Excel spreadsheet was provided in Amendment #9 and updated in Amendment #26 (responses to CMC IRs of 17JAN2020 and 050MAR2020, respectively). Information provided in this spreadsheet was used for specification setting, and is acceptable.*

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Kite Pharma requests a categorical exclusion from environmental assessment of KTE-X19 under 21 CFR 25.31(c). Risk assessments for potential release of the (b) (4) retroviral vector and for viability and degradation of KTE-X19 in the natural environment are provided and are summarized as follows.

The (b) (4) retroviral vector encodes only the (b) (4) . The majority of the native gamma-retrovirus sequence is not present. The vector therefore does not encode any of the elements required for viral replication, rendering it replication incompetent by design. The viral genes required to produce retroviral particles (i.e., gag, pol and env) are contained only in the packaging cell line. Thus, the potential risk of RCR production is minimized, as three independent recombination events would be required to generate a functional, replication competent virus. The (b) (4) are tested for RCR and found negative. RCR has not been detected in vector production lots or clinical trials with this or other similar vectors. The risk of RCR formation is therefore assessed to be negligible.

In the event of accidental release of vector into the environment, one possible concern would be recombination with a similar wild type retrovirus. This would require co-infection of the same cell with both vector and wild-type virus. Efficient transduction of host cells by the (b) (4) vector requires the presence of a reagent (such as (b) (4)) to facilitate vector adsorption to the cells, making this first step in transduction unlikely outside of controlled conditions. Secondly, retroviruses have evolved to be transmitted via blood and body fluids and retroviral particles are not stable when exposed to environmental conditions, such as desiccation, elevated temperatures, UV light, or pH changes. If released into an aqueous environment (such as waste water) that is abundant with heterotrophic microorganisms and organic particles, it is expected that retroviral particles will be either degraded by microorganisms or rapidly adsorbed onto particles. Finally, even if the very improbable co-infection and recombination events occur, the CAR transgene is not expected to confer a selective advantage to any hypothetical recombinant retrovirus, making propagation in the environment unlikely.

There is negligible risk to the environment from release of KTE-X19. Residual (non-integrated) (b) (4) retroviral vector is cleared from KTE-X19 (as outlined in Section 3.2.A.2.3 Control of Adventitious Agents in the production of KTE-X19). There are no known mechanisms that would enable shedding of vector from KTE-X19, and the cells themselves are not spontaneously shed into the environment via excreta (saliva, urine, feces). Patient samples (blood, bone marrow, or lymph node biopsies) may contain viable KTE-X19, but like normal human T cells, KTE-X19 requires controlled conditions (defined culture media, a narrow pH and osmolality range, appropriate humidity and temperature) to proliferate outside the body, and will not survive in the environment due to the fragile nature of mammalian cells which are sensitive to environmental conditions. KTE-X19 will be rapidly destroyed by standard means of disinfection (e.g., bleach, alcohol, detergents, soap) and will be administered in hospitals, institutions, and/or specialized clinics. Used product bags will be disposed of according to biologic waste management procedures; unused product will not be disposed in the sewer system. Administration of KTE-X19 to the patient occurs via closed system, minimizing the risk of spills. In the event of accidental injection (e.g., via needlestick incident) to healthcare providers, the immune system of the recipient would be expected to eliminate KTE-X19 (due to HLA mismatch) although treatable transient local or allergic reactions could occur. No long-term negative consequences are expected in this case.

Risk mitigation procedures for KTE-X19 include use of universal precautions for prevention of transmission of blood-borne infections, and established procedures for handling live human cells (per institutional policies). All personnel involved in handling or administration of KTE-X19 are trained (per site qualification procedures) to adhere to safe practices. Work surfaces will be decontaminated according to hospital/facility procedures, and a spill kit containing absorbent material and an appropriate disinfectant will be available during receipt and administration of the product. The used IV bag and tubing will be discarded as biohazardous waste after administration is complete, and the room will be subject to routine cleaning and disinfection procedures.

Reviewer assessment: *The rationales provided by Kite are acceptable to conclude that KTE-X19 poses a negligible risk to the environment or to the general public. The potential for vector recombination to a replication competent form is assessed as extremely low to negligible. The potential for the vector or KTE-X19 to persist in the environment is*

negligible. There is a potential risk for exposure of healthcare staff during product administration, but this can be effectively mitigated by universal precautions that are already established at healthcare facilities and by additional training provided by Kite during treatment site qualification. Overall, there are no significant environmental or public health impacts posed by the (b) (4) *vector or by KTE-X19. Categorical exclusion under 21 CFR 25.319(c) is acceptable.*

B. Labeling Review

Full Prescribing Information (PI):

Prescribing information (PI) is modeled closely on that previous established for YESCARTA, as outlined in Table 126 below.

Table 126. Prescribing information

Full PI section	Assessment
3 Dosage Forms and Strengths	Information (other than tradename) is identical to YESCARTA.
11 Description	Includes the following information regarding the (b) (4) enrichment step: *"The manufacture of TECARTUS includes a T-cell enrichment step that may reduce the likelihood of circulating CD19 expressing tumor cells in patients' leukapheresis material driving the activation, expansion, and exhaustion of the anti CD19 CAR T cells during the ex vivo manufacturing process."* *This is acceptable.* Information regarding the use of both anti-CD3 and anti-CD28 antibodies was added in response to FDA comments. *This is acceptable.*
16 How Supplied/Storage and Handling	Information is identical to YESCARTA (other than tradename and NDC numbers). *This is acceptable*

Reviewer comment: *Edits were made to the draft PI label to reflect the use of both anti-CD3 and anti-CD28 mAbs during the T cell activation process. These changes were communicated to the applicant on 15JUN2020, and accepted in the revised labeling provided in amendment #52, received 24JUN2020. There are no outstanding CMC concerns regarding prescribing information content.*

Container label

Copies of the patient and product labels to be affixed to the KTE-X19 final product container closure (b) (4) bag) are shown in Figure 53.

Figure 53. KTE-X19 patient ID and product labels for final product container closure

Figure 53. Final product infusion bag labels containing patient (left) and product (right) information. Note that the pink borders are dye lines and will not be present in the final labels.

A machine-readable 2-dimensional barcode (comprising the NDC [71287-219-01] and lot number) is provided on the patient label. Human-readable information including lot number, expiration date, patient name (first, middle initial, last), patient ID, date of birth, and hospital patient ID number, and donor identification number (with barcode) is also provided on the patient ID label.

The 10-digit (5-3-2 format) NDC barcode for the final product bag is included on the product label (common between lots). Within the NDC barcode, the Labeler code (71287) was cross-checked with the NDC/NHRIC labeler code site and corresponds to Kite Pharma, Inc. Information regarding manufacturer, contents, dose, storage, precautions, thawing, mixing, and administration is also provided on the product label.

Reviewer comment: *Updated patient and product bag labels, including the tradename (TECARTUS™) and non-proprietary name (brexucabtagene autoleucel) with font sizes aligning to 21 CFR 610.62 were provided in Amendment # 48 (response to CMC/Labeling IR of 15MAY2020) received 22MAY2020. Note that the proposed product labels for KTE-X19 differ from those for YESCARTA® in that the KTE-X19 labels have a teal banner, while the YESCARTA® labels have a purple banner. The patient ID labels are similar to YESCARTA®, although the product logos for YESCARTA® and TECARTUS (present on both patient and product labels) differ. The similarities between the labels for these different products are not a concern due to the rigorous COI/COC procedures to confirm patient identity prior to administration, thus these labels are acceptable.*

Cryocassette (package) labels

Copies of the patient ID and product labels (placed on the aluminum cryocassette used to store the infusion bags) are shown in Figure 54 below:

Figure 54. Patient ID and product labels for the cryocassette

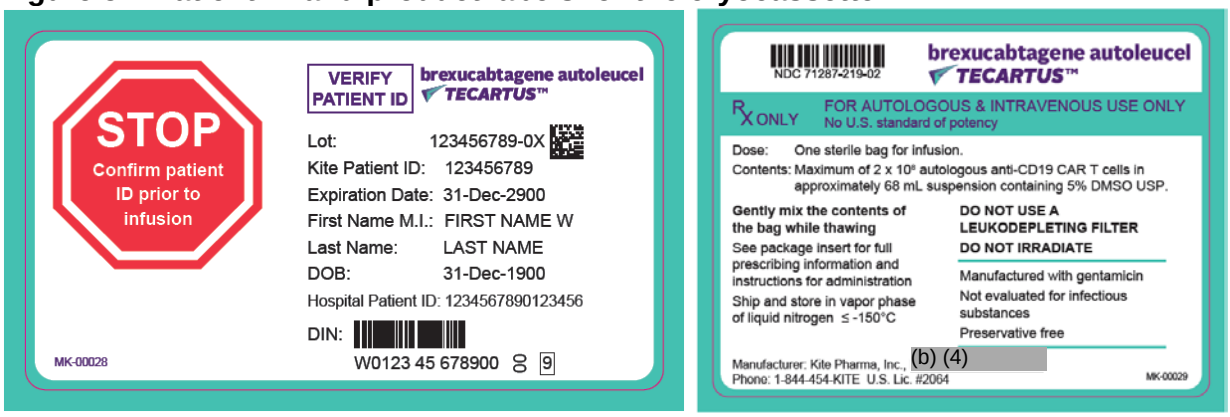


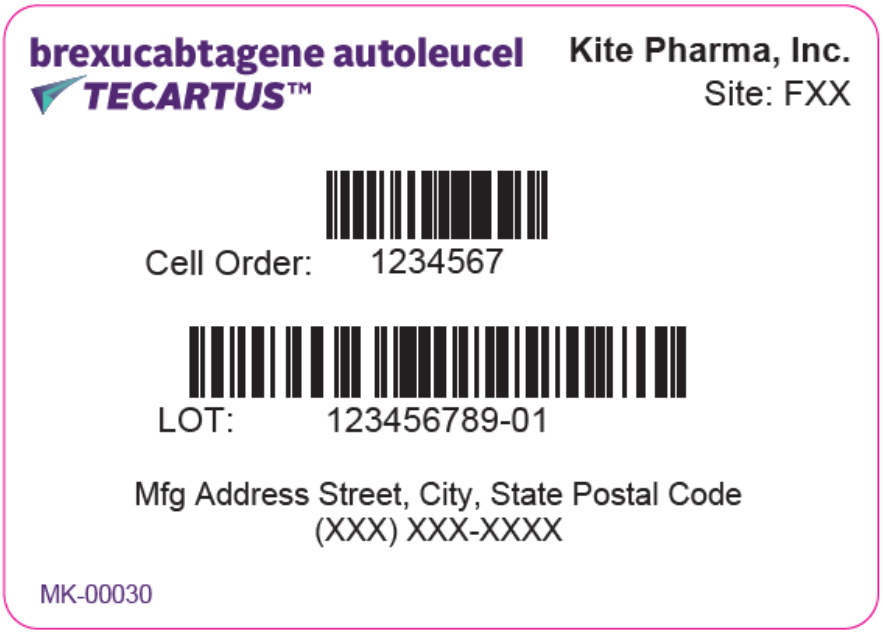
Figure 54. Cryocassette (package) labels containing patient (left) and product (right) information

These labels contain identical information to that on the container closure labels, except for the different NDC (71287-219-02) specific to the package.

Reviewer comment: *Updated cryocassette labels were provided in Amendment # 48 (response to CMC/Labeling IR of 15MAY2020) received 22MAY2020. Note the prominent "STOP" sign reminding personnel to check patient identifiers prior to infusion; this feature distinguishes the cassette label from the bag label. These labels are acceptable.*

The LN2 shipper label is shown in Figure 55 below:

Figure 55. LN2 shipper label



This label is affixed to the dry vapor LN2 shipper, and displays the cell order and lot number but no information that directly identifies the patient.

Reviewer comment: *An updated shipper label was provided in Amendment # 48 (response to CMC/Labeling IR of 15MAY2020) received 22MAY2020. The address and telephone information need to be added to the final version, but this label is otherwise acceptable.*

UNII code
The product unique Ingredient Identifier (UNII) provided by the FDA UNII team is: BREXUCABTAGENE AUTOLEUCEL – UNII:4MD2J2T8SJ.
Reviewer comment: *The original UNII (AXICABTAGENE CILOLEUCEL - UNII: U2I8T43Y7R) provided in Section 1.14.1.3 KTE-X19 SPL was updated to the correct version in Amendment #39 (response to CMC IR of 14APR2020) received 22APR2020. This is acceptable.*

Modules 4 and 5
This section reviewed by GEP
Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Secondary objectives in ZUMA-2 included pharmacokinetics and pharmacodistribution (PK/PD) studies to assess levels of anti-CD19 CAR T cells in blood and levels of cytokines in serum and association with clinical disease (as described in Module 5.3.4.2). The PK and PD assessment methods parallel those used for analysis of the ZUMA-1 study supporting licensure of YESCARTA® in BLA 125643. Assays were performed at Kite Pharma, the (b) (4) , as outlined in the method descriptions. Validation and/or qualification data for these methods is summarized in Module 5.3.1.4 as follows.

Anti-CD19 CAR T cell (b) (4) assay
The (b) (4) assay for anti-CD19 CAR T cells used for analysis of patient peripheral blood samples is based on a method described by (b) (4) and further optimized and validated by (b) (4)
Validation Summary Report SH.CP.CT.val.0026.0001 and addendum). This method was used to (b) (4)

This assay was qualified and validated to address specificity, linearity, range of qualitative and quantitative detection, accuracy, precision (repeatability, robustness and intermediate precision). The assay was deemed specific as anti-CD19 CAR (b) (4) was detected only in samples from subjects expected to be positive and was not detected in any sample known to be negative. The assay linear range was demonstrated over a (b) (4) dynamic range from a starting concentration of (b) (4) . Accuracy was assessed against known positive samples provided by Kite, and results were in agreement between Kite and (b) (4).

(b) (4)

Reviewer comment: *Information regarding assay validation is summarized in Module 5.3.1.4. The assay validation acceptance criteria for the Anti-CD19 CAR T cell* (b) (4) *assay validation study performed at the* (b) (4) *was not provided in the initial submission, but this information (document* (b) (4) *SH.CP.CT.val.0025.0001 - Quantitative* (b) (4) *for Detection and quantitation of CAR19 in PBMC* (b) (4) *using SOP KTE-C19-101.0003.0001) was submitted in Amendment #37 (response to CMC IR of 03APR2020) received 13APR2020. Assay performance met all validation acceptance criteria, indicating that this method is acceptable. Note that* (b) (4) *method for patient monitoring differs from the* (b) (4) *used in lot release testing described in Section 3.2.P.5.3 Validation of Analytical Procedures.*

Cytokine assays

Cytokine evaluations were performed on patient serum samples collected at baseline (prior to pre-conditioning chemotherapy) day 0 (pre-infusion) and days 3, 7, 14, and 28 after KTE-X19 infusion. Unscheduled samples were collected if prolonged treatment-related toxicities or readmission to hospital with any KTE-X19 AE occurred. In some cases, CSF from patients with Grade ≥2 neurologic events was collected and tested. Serum and CSF samples were processed and frozen locally, prior to shipment to (b) (4) for storage at -(b) (4), and shipping to Kite for testing. 17 analytes (pre-selected from a larger panel of 40 analytes) were assessed, as shown in Table 127.

Table 127. Patient cytokine testing

Analyte	Category	Assay	Qualification report(s)	LOQ (pg/ml)
IL-1ra	Inflammatory/Immune modulating	(b) (4)	REP-00259, REP-00380	(b) (4)
IL-2	Homeostatic/proliferative		REP-00257	
IL-2Rα	Inflammatory/Immune modulating		REP-00260, REP-17900	
IL-6	Inflammatory/Immune modulating		REP-00257	
IL-7	Homeostatic/proliferative		REP-00255	
IL-8	Chemokine		REP-00257	
IL-10	Inflammatory/Immune modulating		REP-00257	
IL-15	Homeostatic/proliferative		REP-00255	
IFN-γ	Inflammatory/Immune modulating		REP-00257	
TNF-α	Inflammatory/Immune modulating		REP-00257	
CRP	Inflammatory/Immune modulating		REP-00256	
CXCL10	Chemokine		REP-00258	
Granzyme B	Immune effector		Not qualified	
Perforin	Immune effector		Not qualified	
Ferritin	Other		Not qualified	
ICAM-1	Other (adhesion molecule)		REP-00256	
VCAM-1	Other (adhesion molecule)		REP-00256	

(b) (4)

These cytokine assay methods are all commercially available (b) (4) systems performed per manufacturer's instructions. Assays were qualified (as indicated in Table 127) for accuracy, precision, ruggedness, stability and dilutional linearity, with limits of quantification determined as shown. The assays for (b) (4) were not qualified and used for exploratory purposes only.

Reviewer comment: *The (b) (4) systems (b) (4)) included analytes in addition to those qualified. These analytes were used for exploratory purposes and values are not reported in study reports. All assays were shown to be fit for purpose and are acceptable. There are no concerns.*

B cell aplasia assays

Levels of B cells in PBMC samples were assessed at baseline and months 3, 6, 12,15, 18 and 24 at (b) (4) using a commercially available (b) (4)

.

Reviewer comment: *This assay does not distinguish between normal and leukemic $CD19^+$ $CD20^+$ cells, but this is not a required parameter as KTE-X19 does not discriminate between healthy and malignant cells either. However, as B cells are defined as $CD19^+$ or $CD20^+$ $CD45^+$ cells, it should be able to detect tumors that have lost CD19 expression (through immune escape). This assay has been appropriately validated. There are no concerns.*

Screening ELISA for anti-FMC63 antibodies

Antibodies against the FMC63 scFv portion of the CAR were detected using a (b) (4) ELISA. This assay consist of (b) (4)

. This assay was performed and validated at (b) (4) and is the same method as used for BLA 125643.

Reviewer comment: *Validation and partial re-validation (due to a (b) (4) reports for this method are provided and are acceptable. Note that this assay will detect (b) (4) antibodies.*

Confirmatory cell-based assay to detect antibodies against the extracellular region of the anti-CD19 CAR

Serum from ZUMA-2 patients who tested positive for antibodies against FMC63 in the screening ELISA was tested using a confirmatory cell-based assay. This method used (b) (4)

Central confirmation of diagnosis (b) (4)

Local diagnosis of disease was confirmed at a central CAP/CLIA accredited lab (b) (4) using (b) (4) methods, verified by a pathologist. The following assays were validated:

- (b) (4)

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

Reviewer comment: *Based on the information presented, the* (b) (4) *assays are acceptably validated and fit for purpose. There are no concerns.*

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:
Assay methods used to support secondary endpoints in the ZUMA-2 study are adequately described and either validated or qualified and fit for purpose. Some details regarding assay qualification for the (b) (4) assay to detect KTE-X19 at (b) (4) are not provided (a referenced study report is not included in the submission), but details of assay performance are adequate. (b) (4) assays to confirm diagnosis are suitably validated. There are no outstanding concerns with diagnostic or PK/PD assay methods.