Summary Basis for Regulatory Action

Date: October 18, 2017

From: Michael Havert, PhD, Chair of the Review Committee

BLA #:125643

Applicant Name: Kite Pharma, Incorporated

Date of Submission: March 31, 2017

Goal Date: November 29, 2017

Proprietary Name: YESCARTA™

Proper Name: axicabtagene ciloleucel

Indication: for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

Recommended Action: Approval

Review Office Signatory Authority: Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies

- ☐ **I concur with the summary review.**
- ☐ **I concur with the summary review and include a separate review to add further analysis.**
- ☐ **I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority: Mary A. Malarkey Director, Office of Compliance and Biologics Quality

- ☐ **I concur with the summary review.**
- ☐ **I concur with the summary review and include a separate review to add further analysis.**
- ☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA.

Document title	Reviewer name
Clinical Reviews • *Clinical (product office)* • *OCE Review* • *REMS Memo* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Yvette Kasamon, MD (OCE) Najat Bouchkouj, MD (OTAT/DCEPT) Bindu George, MD (OTAT/DCEPT) R. Angelo de Claro, MD (OCE) Amy McKee, MD (OCE) Adamma Mba-Jonas, MD (OBE/DE) Colonious King (OCBQ/DIS/BMB)
Statistical Review • *Clinical data*	Shiowjen Lee, PhD (OBE) Xue (Mary) Lin, PhD (OBE)
CMC Reviews • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)* • Review of Microbiological Test Methods (*OCBQ/DBSQC/LMIVTS*)	Mike Havert, PhD (OTAT/DCGT) Anna Kwilas, PhD (OTAT/DCGT) Graeme Price, PhD (OTAT/DCGT) Jakob Reiser, PhD (OTAT/DCGT) Don Fink, PhD (OTAT/DCGT) Don Ertel (OCBQ/DMPQ) Wei Wang (OCBQ/DMPQ) Hyesuk Kong, PhD (OCBQ/DBSQC) Marie Anderson, MS, PhD (OCBQ/DBSQC)
Pharmacology/Toxicology Review	Jinhua Lu, PhD (OTAT/DCEPT)
Clinical Pharmacology Reviews • *Clinical Pharmacology* • *Pharmacometrics Consult*	Xiaofei Wang, PhD (OTAT/DCEPT) Chao Liu, PhD (CDER/OCP)
Labeling Review • *APLB (OCBQ/APLB)*	Dana Jones (OCBQ/DCM)

1. INTRODUCTION

Kite Pharma, Inc., submitted a Biologics License Application (BLA), STN 125643, for licensure of axicabtagene ciloleucel. Axicabtagene ciloleucel is a new molecular entity, with the proprietary name of YESCARTA. YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

YESCARTA is comprised of genetically modified, antigen-specific autologous T cells reprogrammed to target cells that express CD19. CD19 is an antigen expressed on the surface of B cells and tumors derived from B cells. The YESCARTA chimeric antigen receptor (CAR) protein has a murine single chain variable fragment (scFv) with specificity for CD19 linked to two signaling domains derived from human CD3-ζ and CD28 genes. The CAR protein plays a critical role in YESCARTA function, including T cell activation and anti-tumor activity.

This document summarizes the basis for regular approval for YESCARTA. A single clinical trial, ZUMA-1, provides the primary evidence of safety and effectiveness for the BLA submission. The recommendation for approval is based on the complete remission rate and duration of response demonstrated in the phase 2 portion of the study. The major risks of YESCARTA include cytokine release syndrome (CRS) and neurologic toxicity, which can be fatal or life-threatening, infections, febrile neutropenia, and prolonged cytopenias.

The review team recommends regular approval of this BLA with postmarketing requirements (PMR) for a Risk Evaluation Mitigation Strategy (REMS) with Elements To Assure Safe Use (ETASU) for the management of CRS and neurologic toxicity, training and assessment of sites and the use of tocilizumab and a postmarketing observational study to primarily assess long-term toxicities of YESCARTA.

2. BACKGROUND

Disease background

DLBCL, which comprises 30-40% of non-Hodgkin lymphomas (NHLs), is fatal if not cured. Approximately half of all patients with aggressive B-cell NHL, such as DLBCL, have relapsed or refractory (rel/ref) disease. High-grade B-cell lymphomas with aberrations in MYC, BCL2 and/or BCL6 are associated with an inferior prognosis, even in the newly diagnosed setting. Patients with untreated rel/ref aggressive B-cell lymphoma have a median survival of approximately 3-4 months. In a recent meta-analysis (SCHOLAR-1 study) of >500 patients with rel/ref aggressive lymphoma, the objective response rate to modern salvage therapy was only 20-30%, complete remission rates were < 15%, and the median overall survival was 6 months.

Available Therapies

There are no approved therapies for patients with rel/ref, aggressive B-cell NHL. High-dose therapy with autologous HSCT is the usual standard for first relapse of *de novo* DLBCL, if the relapse is chemosensitive. Over 50% of such relapses, however, are chemoresistant.

Regulatory History

IND 16278, submitted 12/2014, investigates axicabtagene ciloleucel in aggressive B-cell lymphomas. Axicabtagene ciloleucel was granted orphan designation for DLBCL (3/2014), PMBCL (4/2016), and FL (4/2016) and received Breakthrough Therapy Designation in 12/2015 for refractory, aggressive NHL.

In a Type B pre-BLA meeting in 10/2016, FDA indicated that it was premature to submit a BLA on 12/30/2016 due to <6 month follow-up for efficacy in the ZUMA-1 study and fewer than the prespecified number of subjects in the primary analysis. FDA requested data on response and response duration after 6 months follow-up for all subjects. The Agency agreed to a rolling submission, with a late component on the chain-of-custody/chain-of-identity process validation to be received within 30 days.

The first module was submitted on 12/2/2016 and the final modules on 3/31/2017. After BLA submission, a teleconference was held 5/31/2017 due to inadequate follow-up for efficacy with 12/2016 (Independent Review Committee (IRC)) and 1/2017 (investigator) data cuts. Alignment

was reached to submit updated efficacy data by 6/30/2017, using a 4/26/2017 cut-off date for both investigator and IRC assessments. The PDUFA action due date is 11/29/2017.

3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Product Description

YESCARTA comprises human autologous T cells transduced with a retroviral vector containing a chimeric antigen receptor (CAR) directed against human CD19, an antigen expressed by most B cell malignancies as well as all normal B lymphocytes in peripheral blood and spleen. For production of YESCARTA, a patient's own T cells are harvested and genetically modified e*x vivo* by transduction using a γ-retroviral construct encoding an anti-CD19 CAR (b) (4)). The anti-CD19 CAR consists of a single chain variable region fragment (scFv) derived from a CD19 specific monoclonal antibody, CD28 elements (i.e., (b) (4) and CD3 ζ (b) (4) (b) (4) .

Manufacturing Summary

The manufacturing process begins by enriching the patient's apheresis material for lymphocytes and activating the patient's T cells during a defined culture period in the presence of (b) (4) human IL-2 (b) (4) IL-2) and anti-CD3 antibody (anti-CD3 Ab). The patient's T cells are then transduced with (b) (4) , a retroviral vector expressing an anti-CD19 CAR, and expanded. The manufacturing process is (b) (4) YESCARTA is cryopreserved and stored at not greater than -150°C. YESCARTA is shipped in a vapor phase liquid nitrogen dry shipper (dewar) to the clinical infusion center by a qualified courier. The chain-of-identity of the entire process from leukapheresis to infusion and throughout all manufacturing steps is controlled by a computer-based system to ensure the product's identity and product traceability.

The manufacturing process for the (b) (4) vector involves (b) (4) .

Manufacturing Controls or Control Strategy

Manufacturing process consistency is mainly controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring, (3) in-process control testing, (4) lot release tests, (5) traceability by using a chain-of-identity system, and (6) validation of the manufacturing process. The raw material qualification program consists of risk assessment of the source materials, vendor qualification and audits, and an incoming materials management system that consists of visual examination of the package, identity testing, and confirmation of the certificate of analysis upon receipt of the material. Within individual unit operations of the manufacturing process, critical process parameters were established based on process characterization and manufacturing risk assessment studies during process development stages. The critical process parameters define the acceptable operating ranges for each manufacturing step necessary to ensure a consistent final product that meets the predefined product quality attributes (lot release specifications). While the in-process monitoring activities ensure each

unit operation is on the right track, in-process control testing is used to make appropriate decisions for the next manufacturing steps. Lot release testing serves as the final confirmation of product quality before releasing the product for commercial use.

Process Validation

The commercial manufacturing process for YESCARTA was adapted by Kite from a process originally developed under IND at the (b) (4)
The suitability of the commercial manufacturing process at (b) (4) was assessed using (b) (4) healthy donor lots as a part of process performance qualification (PPQ). The number of PPQ lots was selected based on (b) (4) variability of a sample of donor lots (n=(b) (4) lots are sufficient to assess differences in (b) (4) at a 95% confidence level with (b) (4) power. Testing of PPQ lots during production included a full panel of in-process and final product assessments that include all critical and non-critical process parameters. These test results were compared with prospectively established process validation acceptance criteria (PVAC). PVAC were generated using a tolerance interval approach with a 95% confidence interval and 95 or 99% proportion based on data from (b) (4) healthy donors and (b) (4) clinical subjects. All deviations and exceptional conditions during PPQ studies were investigated and closed. All PPQ studies met the pre-defined PVAC. Additional PPQ and validation studies included media fill, (b) (4) of YESCARTA (b) (4), chain-of-identity/chain-of-custody, shipping, and (b) (4) vector manufacturing. Finally, as a part of process validation, a continuous process verification (CPV) protocol was established to monitor and trend quality information.

Manufacturing Risks, Potential Safety Concerns and Management

Loss of COC/COI

As an autologous product, loss of chain-of-custody (COC)/chain-of-identity (COI) would have a direct impact on patients for whom YESCARTA is prescribed. COC/COI checks were incorporated throughout the manufacturing process and before final product administration. Testing of the integrated systems used to create, control and trace COI and COC for YESCARTA commercial manufacturing processes was included as a separate component of process validation and it was concluded that this system was suitable for its intended purpose.

Replication Competent Retrovirus

Generation of replication-competent retrovirus (RCR) during the manufacturing process for YESCARTA is a theoretical safety concern. To date, no RCR has been detected in any clinical trials using YESCARTA, as tested (b) (4) product with a sensitive (b) (4) RCR assay, or on the (b) (4) product with the same RCR assay or a (b) (4) RCR assay.

Insertional Mutagenesis

Insertional mutagenesis due to vector integration is a potential risk for inducing secondary malignancies following YESCARTA administration. Integration of the vector into the patient's cells might inadvertently activate a cellular proto-oncogene or disrupt a tumor suppressor gene, leading to malignant transformation events. To mitigate the risk of insertional mutagenesis, the average (b) (4) is limited to less than (b) (4)

Specifications

The final lot release specifications are shown in the table below.

Table 1: YESCARTA lot release specifications

Test	Method	Requirement for commercial use
Appearance	Visual inspection	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles.
Identity	(b) (4) for the scFv heavy chain variable region, linker and CD28 sequences	(b) (4)
Dose[1]	Viable cell count/Anti-CD19 CAR expression	(b) (4) anti-CD19 CAR T cells/kg (maximum allowable dose: 2×10^8 anti-CD19 CAR T cells)
Potency	Cell viability	(b) (4)
	Anti-CD19 CAR expression	(b) (4)
	(b) (4)	(b) (4)
Purity	(b) (4)	(b) (4)
	Gentamicin	(b) (4)
	Endotoxin	(b) (4)
Microbiological tests	Mycoplasma (b) (4) method	Negative
	Sterility	No growth
Testing for Retrovirus	RCR by (b) (4)	Negative
	RCR (b) (4)	Negative[2]
(b) (4)	(b) (4) for the scFv heavy chain variable region, linker and CD28 sequences	(b) (4)

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

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

Impurity profile

YESCARTA consists of CD3+ T cells, which typically make up greater than (b) (4) of the total cell population. The mean (b) (4) with the (b) (4) vector is about (b) (4) of total cells in the final product with a standard deviation of about (b) (4)

Impurities can be classified into product-related (cellular impurities) and process-related impurities. Cellular impurities are those derived from leukapheresis material such as red blood cells, granulocytes, dead cells, and B cells/B-lineage lymphoblasts. Process-related impurities include ancillary materials and reagents that are not intended to be present in the final product.

Cell viability is a lot release specification with an acceptance criterion of (b) (4) . Cell viability is controlled during the manufacturing and formulation process, and the percentage of total live cells in YESCARTA has been consistently above the acceptance criterion.

The frequency of different non-CD3+ T cell populations has been characterized during development and these data demonstrate a (b) (4) frequency range of NK cells (b) (4)) and NK T cells (b) (4)) and a very (b) (4) frequency range of dendritic cells (b) (4) , monocytes (b) (4) , and B cells (b) (4)).

Kite Pharma has evaluated clearance levels for (b) (4) , Gentamicin, (b) (4) . Overall the results of the impurity clearance evaluation demonstrated a greater than (b) (log clearance of process-related impurities prior to final product formulation. The manufacturing process contains (b) (4) . The overall theoretical clearance of process-related impurities after (b) (4)) is expected to be greater than (b) (4)

Viral safety

The potential risks from adventitious viral agents for YESCARTA are addressed through assessment of source materials and testing programs during (b) (4) vector and YESCARTA manufacturing. Animal and human or recombinant technology-derived raw materials are qualified and tested for their origin and suitability to minimize potential contaminations with various adventitious viruses and potential TSE/BSE risk. Therefore, the infusion of YESCARTA presents an overall low risk of patient infection from viral adventitious agents.

Container closure-DP

YESCARTA final drug product is filled and cryopreserved at ≤ -150°C in (b) (4) (b) (4) freezing bags, as a single-dose cell suspension, which is thawed prior to infusion. The (b) (4) freezing bags are 510(k) cleared devices ((b) (4)

The container closure integrity (CCI) of the bags is tested by the vendor (b) (4) In addition, all the cryobags (100%) are inspected by the vendor for leaks.

Additional CCI testing (CCIT) is performed by Kite on the (b) (4) filled cryobags using the (b) (4) (b) (4)). Kite reports a satisfactory CCIT qualification.

Once filled and sealed, each (b) (4) cryobag is placed into an aluminum cassette to provide protection during storage, shipment, and handling.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release, with no requirement for submission of lot release protocols or product samples to CBER. The basis for this decision is that YESCARTA is an autologous product; each lot will treat a single patient. Lot release testing would negatively impact the often-limited quantity of cells available to the patient and failure of a single lot will have a minimal potential impact on public health.

c) Facilities review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of YESCARTA are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 2: Manufacturing facilities

Name/Address	FEI number	DUNS number	Inspection /Waiver	Justification /Results
Kite Pharma, Inc. 2355 Utah Avenue El Segundo, California, 90245 • Manufacture, control, and storage of YESCARTA Final Product • All YESCARTA Final Product release testing, • (b) (4) Vector release and stability testing per specifications • (b) (4) Vector lot disposition	3012583739	080315797	Pre-License Inspection	CBER June 12-16, 2017 VAI
(b) (4) • Manufacture, control, packaging, labeling, and storage of (b) (4) Vector	(b) (4)	(b) (4)	Pre-License Inspection	CBER (b) (4) VAI
(b) (4) • Alternate location for final product release testing	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI

CBER performed a Pre-License Inspection (PLI) at Kite Pharma, Inc. in El Segundo, CA from June 12-16, 2017 for the manufacture of YESCARTA. At the end of the inspection, CBER issued a Form FDA 483. The firm responded to the observations, and the corrective actions were reviewed and found to be acceptable. All inspectional issues were resolved.

CBER also performed a PLI at (b) (4) a contract manufacturing organization (CMO) responsible for manufacturing of the retrovirus vector (b) (4)). The inspection was conducted (b) (4) . CBER issued a Form FDA

483 at the end of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be acceptable. All inspectional issues were resolved.

FDA's Office of Regulatory Affairs (ORA) performed a routine surveillance inspection of (b) (4) from (b) (4) The inspection was classified as No Action Indicated.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration or distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

A site-to-site comparability study was conducted for each manufacturing facility producing clinical products under IND, including products made at (b) (4) and the facility used to make commercial products ((b) (4) Each of these studies demonstrated that CD19 CAR-positive T cells manufactured by all facilities were comparable.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

(b) (4) A subsequent co-culture study of anti-CD19 CAR T cells derived from peripheral blood mononuclear cells obtained from patients with NHL demonstrated CD19-specific induction of multiple cytokines, chemokines, and effector molecules.

To evaluate CD19-specific anti-tumor activity *in vivo*, an analogous murine CAR construct recognizing the murine CD19 molecule was evaluated in a lymphodepleted syngeneic mouse model of CD19+ B cell lymphoma. Following intravenous injection of murine T cells expressing the anti-murine CD19 CAR into the mice, tumors were eliminated (i.e., lymphoma cells were undetectable) and animal survival was extended. However, depletion of normal B cells (i.e., B cell aplasia) also occurred, but no effect on overall animal health was observed (Kochenderfer JN, et al. Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. Blood. 2010; 116(19):3875-86).

No *in vitro* or *in vivo* genotoxicity and carcinogenicity assessments for YESCARTA were conducted. To address the risk of retroviral vector insertional mutagenesis and potential carcinogenicity/tumorigenicity, the Applicant performed a review of published nonclinical and clinical information reported for T cells transduced with retroviral vectors. The data suggest that T cells are relatively resistant to malignant transformation by retroviral vectors.

No animal developmental and reproductive toxicity (DART) studies were conducted with YESCARTA to assess whether the product can cause embryo or fetal harm when administered to women of childbearing potential.

5. CLINICAL PHARMACOLOGY

Based on pharmacokinetic (PK) analysis of YESCARTA, the following conclusions can be drawn from the study:

- Following infusion of YESCARTA in patients with relapsed or refractory large B-cell lymphoma, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near-baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after YESCARTA infusion.
- After infusion, the median values of Cmax and $AUC_{(0\text{-}28d)}$ of anti-CD19 CAR T cells in responders (CR and PR) were about 2-fold of Cmax and $AUC_{(0\text{-}28d)}$ in non-responders.
- Subjects with Grade 3 or higher neurologic events had significantly higher anti-CD19 CAR T cells expansion (Cmax and $AUC_{(0\text{-}28d)}$) compared to subjects with Grade 2 or lower neurologic events.
- Compared to subjects with Grade 2 or lower neurologic events, subjects with Grade 3 or higher cytokine release syndrome (CRS) had higher anti-CD19 CAR T cells $AUC_{(0\text{-}28d)}$, but not for peak levels of anti-CD19 CAR T cells.
- Age (range: 23 – 76 years old) and gender had no significant impact on $AUC_{(0\text{-}28d)}$ and Cmax of anti-CD19 CAR T cells.
- Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with YESCARTA. Anti-CD19 CAR T cells continued expansion in subjects who received tocilizumab and corticosteroids after infusion of YESCARTA.
- After YESCARTA infusion, peak levels and $AUC_{(0\text{-}28d)}$ of several biomarkers were significantly higher in subjects with Grade 3 or higher neurologic events than subjects with Grade 2 or lower neurologic events. These biomarkers include IL-15, IL-6, IL-2Rα, IL-8, IL-10, IFN-γ, TNF-α, IP-10, IL-2, ferritin, and IL-1RA.
- Significantly elevated peak levels and $AUC_{(0\text{-}28d)}$ were reported in subjects who developed Grade 3 or higher CRS compared to subjects with Grade 2 or lower CRS for the following biomarkers: IL-15, IL-6, IL-2Rα, IL-10, IFN-γ, TNF-α, Granzyme B, IP-10, and IL-1RA.
- Infusion of YESCARTA induced B-cell aplasia in majority of the treated subjects.
- There was no RCR in the blood of YESCARTA treated subjects.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The ZUMA-1 study forms the basis for the review team's recommendation for regular approval of YESCARTA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

Study Description

ZUMA-1 is a single-arm, open-label, multicenter phase 1/2 study for refractory aggressive B-cell NHL, with a primary endpoint of objective response rate (ORR) per investigator after a single infusion of YESCARTA preceded by cyclophosphamide/fludarabine lymphodepleting chemotherapy. The study enrolled adult patients with aggressive B-cell NHL that was primary refractory, refractory to second or greater line of therapy, or relapsed within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The primary efficacy analyses involved the modified intention-to-treat (mITT) population, defined as all patients treated with at least 1.0 x 10^6 CAR-positive T cells/kg. Secondary endpoints included best overall response, DOR, response metrics per independent review committee (IRC), survival, and safety. Notably, ZUMA-1 did not permit bridging therapy between leukapheresis and conditioning.

Clinical Efficacy Findings

In the phase 2 portion, 101 of 111 patients who underwent leukapheresis received YESCARTA. The median time from leukapheresis to product delivery was 17 days (range 14 – 51 days). Most patients (74%) had de novo DLBCL, and 32% had double- or triple-hit lymphoma. The median age was 58 with 24% being aged ≥ 65; the median number of prior therapies was 3; 77% had refractory disease to a second or greater line of therapy; and 21% had relapsed within 1 year after autologous HSCT. Efficacy findings are discussed below.

Primary Efficacy Endpoint

ORR in the mITT and ITT populations is summarized in the table below. Concordance in ORR between investigator and IRC was 79%.

Table 3: Overall Response after One Dose of YESCARTA

Parameter	Phase 2 mITT population (N = 101)		Phase 2 full analysis set (N = 111)	
	Investigator	IRC	Investigator	IRC
Objective response, n (%)	84 **(83%)**	73 **(72%)**	**76%**	**66%**
(95% CI)	(74, 90)	(62, 81)	(67, 83)	(56, 75)
Best response, n (%)				
CR	55 **(54%)**	52 **(51%)**	**50%**	**47%**
(95% CI)	(44, 64)	(41, 62)	(40, 59)	(37, 57)
PR	29 (29%)	21 (21%)	25%	19%
(95% CI)	(20, 39)	(13, 30)	(18, 35)	(12, 27)
Stable disease	19 (19%)	19 (19%)	17%	17%
Progressive disease	5 (5%)	7 (7%)	5%	6%
Not evaluable	2 (2%)	2 (2%)	11%	11%

Source: FDA clinical reviewer
CR, complete remission; PR, partial remission; mITT, modified intention-to-treat; IRC, independent review committee

Secondary Endpoints

Duration of response (DOR) per IRC is summarized in the table below. With an estimated 7.9-month follow-up for DOR, the estimated median DOR was 9.2 months (95% CI: 5.4, NE). Evaluation of DOR remains limited by the large amount of censoring before 6 months.

Response durations tended to be substantially longer in patients with a best overall response of CR, as compared to a best overall response of PR. Among patients achieving CR, the estimated median DOR had not been reached (95% CI: 8.1 months, NE), whereas the estimated median DOR among patients in PR was only 2.1 months (95% CI: 1.3, 5.3).

Table 4. Duration of Response

Outcome per IRC	**Phase 2 mITT population (N = 101)**	
	IRC	
Number of responders	73	
DOR (months),[a] censored for HSCT		
Estimated median (95% CI)	9.2	(5.4, NE)
# censored for DOR	44/73	(60%)
Follow up for DOR (months)		
Estimated median (95% CI)	7.9	(6.2, 9.6)
DOR if BOR is CR (months)		
Estimated median (95% CI)	NE	(8.1, NE)
# censored for DOR	36/52	(69%)
DOR if BOR is PR (months)		
Estimated median (95% CI)	2.1	(1.3, 5.3)
# censored for DOR	8/21	(38%)

Source: FDA clinical reviewer
[a] Kaplan-Meier estimate. DOR was censored for HSCT in remission.
IRC, independent review committee; mITT, modified intention-to-treat; HSCT, hematopoietic stem cell transplantation; DOR, duration of response; NE, not estimable; BOR, best overall response; CR, complete remission; PR, partial remission

Efficacy Review Issues

Inadequate follow-up for efficacy was a major review issue. The initial BLA submission had different data cuts for IRC and investigator assessments, with both having an excessive amount of early censoring for DOR. A teleconference was held 5/2017, and the Applicant agreed to submit updated efficacy data, which are the basis of the review. Additionally, errors in the efficacy datasets, in particular with respect to censoring for DOR and PFS, required multiple information requests to resolve.

Efficacy Conclusion

The submitted data provide sufficient evidence of effectiveness for adult patients with large B-cell lymphoma that relapsed within one year of autologous HSCT or was refractory to second- or later-line salvage therapy. This conclusion is based on CR rate and DOR, as determined by the IRC, in 101 patients with particularly poor-risk disease. This benefit is clinically meaningful,

and the overall benefit/risk is acceptable in this population having few, if any, other treatment options.

However, the Applicant sought a broad indication for patients with relapsed/refractory aggressive B-cell NHL, without a specified minimum number of prior lines of therapy, and characterized the intended population as "ineligible for autologous SCT". The data do not support the Applicant's proposed indication, as a) "aggressive B-cell NHL" includes a multitude of diseases that were not studied in ZUMA1; b) ineligibility for autologous HSCT was not the eligibility criterion; and c) only two patients received YESCARTA after failure of 1 prior line of therapy.

Bioresearch Monitoring

Bioresearch Monitoring inspections were issued for three domestic clinical study sites that participated in the conduct of ZUMA-1. The inspections did not identify any problems that impact the data submitted in this BLA.

b) Pediatrics

There are no pediatric data in the intended population. The application does not trigger Pediatric Research Equity Act (PREA), as YESCARTA has orphan designation.

c) Other Special Populations

None.

7. SAFETY

The primary safety population for ZUMA-1 included a total of 108 patients who were treated with YESCARTA (seven patients from Phase 1 and 101 patients from Phase 2). All patients experienced at least one adverse event (AE) following YESCARTA infusion. Ninety-four percent (n=102) experienced Grade 3 or higher events. Serious adverse events (SAEs) were observed in 56 (52%) of patients, and SAEs Grade 3 or higher occurred in 48 (44%) patients. Adverse events of special interest (AESI) included CRS, neurologic toxicities, serious infections, febrile neutropenia, prolonged cytopenias lasting greater than 30 days, and hypogammaglobulinemia. CRS was reported and graded as per Lee 2014 criteria. Serious or fatal events of cerebral edema were reported in the 120-day safety update report.

The table below summarizes the adverse events of special interest.

Table 5. Adverse Events of Special Interest

Study ZUMA-1 N=108	All Grades N (%)	Grades ≥3 N (%)
CRS	101 (94%)	14 (13%)
Neurologic Toxicities*	94 (87%)	34 (31%)
Serious Infections	41 (38%)	25 (23%)
Febrile Neutropenia	39 (36%)	35 (32%)
Prolonged cytopenia not resolved by Day 30	-	30 (28%)
Hypogammaglobulinemia	16 (15%)	0

Source: FDA clinical reviewer
*98% of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion

The following table summarizes the most frequent AEs that were observed following YESCARTA infusion in ≥10 of patients.

Table 6. Most Frequent Adverse Events Occurring in ≥10% of Patients

Body System Organ Class	Preferred Terms*	All Grades N (%)	Grades ≥3 N (%)
Cardiac disorders	Tachycardia	62 (57%)	2 (2%)
	Arrhythmia	25 (23%)	8 (7%)
Gastrointestinal disorders	Diarrhea	41 (38%)	4 (4%)
	Nausea	37 (34%)	0 (0%)
	Vomiting	28 (26%)	1 (1%)
	Constipation	25 (23%)	0 (0%)
	Abdominal Pain	15 (14%)	1 (1%)
	Dry Mouth	12 (11%)	0 (0%)
General disorders	Fever	93 (86%)	17 (16%)
	Fatigue	50 (46%)	3 (3%)
	Chills	43 (40%)	0 (0%)
	Edema	21 (19%)	1 (1%)
Immune system disorders	Cytokine Release Syndrome#	101 (94%)	14 (13%)
	Hypogammaglobulinemia	16 (15%)	0 (0%)
Infections	Infections-Pathogen unspecified	28 (26%)	17 16%)
	Viral infection	17 (16%)	4 (4%)
	Bacterial infection	14 (13%)	10 (9%)
Investigations	Weight Decreased	17 (16%)	0 (0%)
	Dehydration	12 (11%)	3 (3%)
Metabolism and nutrition disorders	Decreased Appetite	48 (44%)	2 (2%)
Musculoskeletal and connective tissue disorders	Motor Dysfunction	20 (19%)	1 (1%)
	Pain in Extremity	18 (17%)	2 (2%)
	Back Pain	16 (15%)	1 (1%)
	Muscle pain	15 (14%)	1 (1%)
	Arthralgia	11 (10%)	0 (0%)
Nervous system disorders	Encephalopathy	62 (57%)	31 (29%)
	Headache	48 (45%)	1 (1%)
	Tremor	34 (31%)	2 (2%)
	Dizziness	22 (21%)	1 (1%)
	Aphasia	19 (18%)	7 (6%)
Psychiatric disorders	Delirium	18 (17%)	7 (6%)
Renal and urinary disorders	Renal Insufficiency	13 (12%)	5 (5%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	35 (32%)	12 (11%)
	Cough	32 (30%)	0 (0%)
	Dyspnea	21 (19%)	3 (3%)
	Pleural Effusion	14 (13%)	2 (2%)
Vascular disorders	Hypotension	62 (57%)	16 (15%)
	Hypertension	16 (15%)	6 (6%)
	Thrombosis	11 (10%)	1 (1%)

Source: FDA clinical reviewer
*FDA group preferred terms

The following events were also counted in the incidence of CRS: Tachycardia, Arrhythmia, Fever, Chills, Hypoxia, Renal insufficiency, and Hypotension

Overall, 34 deaths were reported from the time of informed consent to the data cut-off for the study (January 27, 2017). Thirty patients died of progressive disease and four deaths were attributed to the product as per FDA analysis. Three deaths occurred within 30 days of YESCARTA infusion. Fatal cases of CRS and neurologic toxicity have occurred after receiving YESCARTA.

The median time to onset for CRS was 2 days (range 1 to 12 days), and the median time to resolution was 7 days (range for CRS duration: 2 to 58 days). Manifestations of CRS included fever, hypotension, tachycardia, hypoxia, and chills. Serious events included cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Forty-five percent (49/108) of patients received tocilizumab for CRS management.

The median time to onset of neurologic toxicity was 4 days (range 1 to 43 days). The median duration was 17 days. Prolonged encephalopathy lasting up to 173 days was noted. Most common neurologic toxicities included encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia and anxiety. Neurologic toxicities were managed with supportive care and/or corticosteroids. Almost all Grade ≥ 2 neurologic toxicities occurred within 7 days following YESCARTA infusion.

Successful treatment with YESCARTA resulted in acquired hypogammaglobulinemia due to the loss of normal B cells. Patients were maintained on supplemental treatment with intravenous gamma globulin.

YESCARTA is a genetically modified product that has the potential for integration of the retroviral vector (insertional mutagenesis), replication competent retrovirus, clonal outgrowth, or neoplastic transformation of transduced host cells.

Grade 3 or 4 laboratory abnormalities occurring in ≥10% of patients included: lymphopenia (100%), neutropenia (93%), anemia (66%), thrombocytopenia (58%), hypophosphatemia (50%), hyponatremia (19%), increased uric acid (13%), increased direct bilirubin (13%), hypokalemia (10%) and increased alanine aminotransferase (10%).

The ZUMA-1 protocol required mandatory hospitalization on the day of YESCARTA infusion for all patients and for a minimum of seven days post-infusion. The median duration of hospitalization was 13 days (95% CI 12, 14). The observed range of the duration of hospitalization was 7 to 62 days. Thirty-nine percent of patients remained hospitalized on Day 14.

Risk Evaluation Mitigation Strategies (REMS):

During the conduct of the ZUMA-1 study, fatal and life-threatening adverse events attributed to YESCARTA were mitigated by mandated site and investigator training, careful site selection and monitoring, and instructions for early detection and management of the most serious complications. The fatal and life-threatening adverse reactions warrant warnings, including a boxed warning for CRS and neurologic toxicity. FDA determined that a REMS is indicated to ensure that the benefits of YESCARTA outweigh the risks of CRS and neurologic toxicity. The REMS includes ETASU to mitigate the known risks of CRS and neurotoxicity by:

- Ensuring that hospitals and their associated clinics that dispense YESCARTA are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring those who prescribe, dispense, or administer YESCARTA are aware of how to manage the risks of CRS and neurologic toxicities.

The REMS ETASU requires Kite to ensure that:

- Pharmacies, practitioners and hospitals dispensing YESCARTA are certified through a live training program and knowledge assessment.
- Sites report all cases of CRS and neurologic toxicities.
- Kite maintains documentation that processes and procedures are followed for the YESCARTA REMS program.
- Kite conducts audits to ensure that training processes and procedures are in place.
- Sites verify that a minimum of two doses of tocilizumab are available on site prior to YESCARTA infusion.

Materials provided as part of the REMS included:

- YESCARTA REMS Program Live Training for Hospitals
- YESCARTA REMS Program Knowledge Assessment
- YESCARTA REMS Program Hospital Enrollment Form
- YESCARTA REMS Program Website
- YESCARTA REMS Program Patient/Caregiver Wallet Card

The review team extensively discussed the patient monitoring element of the REMS. Consideration was given to inclusion of a requirement for in-patient monitoring for 7 days following infusion of YESCARTA. However, the final decision was that patients should be monitored at least daily for 7 days at the certified health care facility following infusion for signs and symptoms of CRS and neurologic toxicities.

The theoretical concerns include an increased risk of secondary malignancy due to RCR or insertional mutagenesis. There were no events of RCR infection or insertional mutagenesis reported in the BLA.

Long-term safety after treatment with YESCARTA, particularly from the risk of insertional mutagenesis-related secondary malignancies, remain a concern due to the limited follow-up duration. Therefore, a postmarketing requirement (PMR) study is warranted. As a PMR, the Applicant agreed to conduct an observational registry study that will collect safety information for patients treated with marketed product, including key early adverse reactions and follow-up for 15 years for detection and evaluation of second malignancies. No routine collection of samples to evaluate for RCR is planned as part of this study.

Postmarketing Requirements

Postmarketing Requirement (PMR) Study

The Applicant will conduct a multicenter, prospective, observational safety study using a registry design. The study will include 1500 subjects enrolled within 3 months of the YESCARTA infusion over a period of 5 years. All enrolled subjects will be followed for 15 years from their YESCARTA infusion. Patients will receive clinical evaluation and follow-up according to standard of care for patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. The primary endpoint will be evaluation for secondary malignancy which will include tissue

work-up by the Applicant for these events. Secondary endpoints will be adverse events of CRS and neurologic toxicities and disease outcomes (survival).

The timetable for the PMR study:

Final Protocol Submission: December 22, 2017
Study Completion: December 30, 2037
Final Report Submission: December 22, 2038

8. ADVISORY COMMITTEE MEETING

This application was not presented to an Advisory Committee, because YESCARTA is not the first biologic in its class, and there were no critical review issues that required input from an Advisory Committee.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable

10. LABELING

The proposed proprietary name, YESCARTA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on May 8, 2017 and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on June 29, 2017.

The APLB found the prescribing information (PI), package, and container labels to be acceptable from a promotional and comprehension perspective. The review committee negotiated revisions to the PI, including the INDICATIONS statement and BOXED WARNINGS for cytokine release syndrome and neurologic toxicity. All issues were acceptably resolved after exchange of information and discussions with the Applicant. No issues were identified with the proposed package and container labeling.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the magnitude and durability of the treatment effect and the high unmet medical need, the review team recommends regular approval of YESCARTA on the basis of ZUMA-1. In contrast to the Applicant's proposed indication statement, the clinical review team recommends approval for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma. There is consensus among the review team for this regulatory action.

b) Risk/ Benefit Assessment

Efficacy of YESCARTA was based on complete remission (CR) rate and duration of response. Of 101 patients evaluated for efficacy, the objective response rate was 72%, with a CR rate of 51%, as determined by an independent review committee. With a median follow-up of 7.9 months, the

estimated median duration of response was 9.2 months overall and was not reached in patients achieving CR.

The risks of YESCARTA relate to its mechanism of action, which is the activation of T cells and the destruction of CD19+ B cells, both tumor cells and normal B cells. Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in 94% of the patients. Neurologic toxicities, including fatal or life-threatening reactions, occurred in 85% of the patients. Hypogammaglobulinemia following YESCARTA occurred in 15% of patients and required monitoring and intervention.

The Prescribing Information (PI) will include a boxed warning for CRS and neurologic toxicity and a REMS with ETASU to ensure that the product's benefits outweigh the risks.

The review of the BLA clinical and safety data provides a favorable risk/benefit profile considering the lack of available therapies for heavily pretreated patients with relapsed/refractory large B-cell lymphoma. The review team recommends regular approval of YESCARTA at the dose of 2×10^6 per kg of body weight CAR-positive viable T cells, with a maximum dose of 2×10^8 CAR-positive viable T cells. A postmarketing requirement (PMR) study to assess long-term toxicities of YESCARTA will be conducted.

c) Recommendation for Postmarketing Activities

Marketing approval should include a postmarketing requirement (PMR) that the Applicant conduct a multicenter, prospective, observational safety study using a registry design. The study will include 1500 subjects who will be followed for 15 years after their YESCARTA infusion. The primary endpoint will be evaluation for secondary malignancy, which will include tissue work-up for these events.

<u>The timetable for the PMR study:</u>

Final Protocol Submission: December 22, 2017
Study Completion: December 30, 2037
Final Report Submission: December 22, 2038