

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)**

MEMORANDUM

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Subject: Review of Pharmacovigilance Plan, Post Marketing Requirement, and Risk Evaluation and Mitigation Strategy

Sponsor: Kite Pharma, Inc.

Product: YESCARTA®; axicabtagene ciloleucel

Application: BLA/STN 125643/0

Proposed Indication: Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), and DLBCL arising from follicular lymphoma after two or more lines of systemic therapy

Submission Date: March 31, 2017

Action Due Date: October 18, 2017

1. Objective

- The purpose of this review is to assess the applicant's pharmacovigilance plan (PVP), and determine whether any Post Marketing Requirements (PMRs) or a Risk Evaluation and Mitigation Strategy (REMS) are required for YESCARTA®.

2. Product Information

- Product description
YESCARTA® is a genetically-modified autologous immunotherapy being proposed by the sponsor to be indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), and DLBCL arising from follicular lymphoma after two or more lines of systemic therapy. The patient's T cells are extracted by leukapheresis and then modified *ex vivo* using a retroviral vector encoding an anti-CD19 chimeric antigen receptor. These modified cells are infused back into the patient's body, where they bind to the lymphoma cells and normal B cells to promote T-cell expansion, activation and target cell elimination of the lymphoma cells. The patient must receive lymphodepleting chemotherapy prior to receiving YESCARTA®. The intended setting in which the drug is likely to be administered is an inpatient hospital.
- Proposed dosing regimen(s) and formulation(s)
YESCARTA® is a single, one-time treatment with the proposed following dose: 2×10^6 anti-CD19 CAR- T positive viable T cells per /kg body weight (range: (b) (4) cells/kg), with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells.

3. Pertinent Regulatory History

- YESCARTA® was granted Breakthrough Therapy Designation on December 3, 2015.
- YESCARTA® is currently not marketed in any country.

4. Materials Reviewed

Materials reviewed in support of this assessment include:

- Sponsor's pharmacovigilance plan (PVP) (Section 1.16 of 125643/0)
- Sponsor's proposed label (Section 1.14 of 125643/0)
- Sponsor's proposed REMS (Section 1.16 of 125643/0)
- Sponsor's Clinical Summary of Safety (Section 2.7.4 of 125643/0)
- Sponsor's Proposed Post-marketing Study (Section 1.17 of 125643/0)
- Safety issues identified by OTAT Clinical reviewer (Clinical Review memo draft)
- ZUMA-1 IND Long Term Follow Up protocol

5. Pivotal Trial KTE-C19-101 (ZUMA-1)

KTE-C19-101 ("ZUMA-1") is an ongoing single arm, open-label, multicenter phase 1/2 study for refractory aggressive B-cell NHL, with a primary endpoint of objective response rate (ORR) after a single infusion of KTE-C19 preceded by cyclophosphamide/fludarabine lymphodepleting chemotherapy. The study has been conducted at 25 centers, including 13 centers located in the US. Enrollment began April 21, 2015. The data in the original submission was accrued during the period between the start of enrollment and the data cutoff date of January 27, 2017.

The study has been conducted in two phases; Phase 1 assessed safety of the product, and Phase 2 assessed both safety and efficacy. Seven treated patients from Phase 1 and 101 treated patients

from Phase 2 supply the safety data evaluated in this review. The median duration of follow up for safety was 218 days, with a range of nine to 581 days.

During conduct of the ZUMA-1 study, life-threatening and fatal adverse reactions 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. Of note, all subjects were admitted for 7 days of inpatient monitoring following infusion with the product.

Safety issues of special interest identified during review of ZUMA-1 included:

Cytokine Release Syndrome (CRS): CRS clinically manifests when large numbers of lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines, particularly interleukin-6 (IL-6). Manifestations of CRS can include fever and chills, hypotension, kidney injury, cardiac failure, atrial fibrillation, ventricular tachycardia, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. CRS occurred in 101/108 subjects (94%), 13% of whom experienced Grade 3 or higher (severe, life threatening or fatal) CRS. Four subjects died while experiencing CRS. The median time to onset was 2 days (range 1 to 12 days) and the median duration of CRS was 8 days (range for the duration of CRS:1 to 57 days). Forty-five percent (49/108) of subjects were treated with tocilizumab, an IL-6 blocker.

Neurotoxicity: Ninety-four/108 subjects (87%) experienced one or more neurotoxicity events, including 34 subjects (31%) that experienced Grade 3 or higher (severe or life threatening) events. "Neurotoxicity events" included but were not limited to anxiety, aphasia, delirium, dizziness, encephalopathy, headache, insomnia and tremor. Fifty-four/94 (57%) of neurotoxicity events occurred in the setting of CRS. The median time to onset of any neurotoxicity was 5 days (range 1 to 17 days). Treatment for subjects experiencing neurotoxicity was symptomatic and included close monitoring/observation to assure an open airway, seizure prophylaxis, and corticosteroids (dexamethasone).

Cerebral edema: Two cases of cerebral edema associated with CRS were reported in the 120-day safety update submitted by the sponsor on July 31, 2017; these cases were not included in the original submission adverse event documentation. One of these subjects died and is discussed further below.

Febrile neutropenia: Neutropenia was documented in 86/108 (80%) treated subjects. Grade 3 or higher (severe or life-threatening) neutropenia occurred in 79/108 (73%) of subjects, including 35 subjects (32%) exhibiting ≥ Grade 3 febrile neutropenia. Neutropenia is an expected result of lymphodepleting therapy, and many of these events may have been caused by the lymphodepleting chemotherapy prior to receiving YESCARTA®.

Prolonged (>30 days) cytopenia/hypogammaglobulinemia: Cytopenias of Grade 3 or above occurred in 30/108 (28%) of subjects. These cytopenias included 19 subjects exhibiting ≥ Grade 3 thrombocytopenia, 16 subjects exhibiting ≥ Grade 3 prolonged neutropenia, and 3 subjects exhibiting ≥ Grade 3 anemia. Grade 1 or 2 hypogammaglobulinemia occurred in 16/108 (15%) subjects. Grade ≥3 hypogammaglobulinemia was not observed.

Infections: Infections occurred in 41/108 (38%) of subjects. Grade 3 or higher (severe, life threatening, or fatal) infections occurred in 25 (23%) of patients, five of whom had ongoing infections at the time of death. Grade 3 or higher infections with an unknown/unspecified pathogen occurred in 16% of patients, viral infections in 4%, and bacterial infections in 10%; no subjects exhibited \geq Grade 3 fungal infections.

Death: Thirty subjects died during the follow up period due to progression of primary disease (the sponsor assessment of the cause of these deaths were confirmed by clinical reviewer after review of case narratives). Four deaths not attributable to progression of primary disease occurred during the follow up period:

- Subject 101-009-001:** 29-year-old female with Stage 3 DLBCL, died 16 days after infusion of product due to intracranial hemorrhage in the setting of thrombocytopenia and Grade 4 CRS.
- Subject 101-009-007:** 63-year-old male with Stage 4 FL, died 34 days after infusion of product due to anoxic brain injury after a cardiac arrest event and in the setting of Grade 4 CRS.
- Subject 101-003-006:** 66-year-old female with Stage 4 DLBCL, died 40 days after infusion of product due to hemophagocytic lymphohistiocytosis/macrophage activation syndrome in the setting of Grade 3 CRS.
- Subject 101-022-003:** 51-year-old male with Stage 3 FL, died 15 days after infusion of product due to pulmonary embolism.

One additional death not attributable to progression of primary disease was noted in the 120 Day Safety Update; **Subject 101-025-012** was a 21-year-old male with Stage 4B primary mediastinal large B-cell lymphoma (PMBCL) who died nine days after infusion of the product due to cerebral edema/uncal herniation in the setting of Grade 3 CRS.

Secondary malignancy due to replication-competent retrovirus/insertional mutagenesis: Retroviral vectors provide long-term expression of the chimeric antigen receptor (CAR) in T cells. However, use of these vectors is associated with a risk of secondary malignancy or relapse of primary malignancy due to generation of replication-competent retrovirus (RCR) and insertional mutagenesis. No patients developed RCR during the trial or during follow-up, and no events of insertional mutagenesis resulting in secondary malignancy were noted.

6. Pharmacovigilance Plan

Safety issues identified by the sponsor as well as the sponsor’s proposed risk mitigation strategies are summarized in the table below.

Table 1: Sponsor-Proposed Pharmacovigilance Plan (adapted from sponsor’s Pharmacovigilance plan (PVP), Section 1.16 of 125646/0)

	Safety Concern	Pharmacovigilance Action
1	Cytokine Release Syndrome (identified risk)	<ul style="list-style-type: none"> - Routine PV, REMS, boxed warning in PI, severe adverse events (SAE’s) will be followed up on a case-by-case basis - Additional safety information to be derived from long term follow up of clinical trial ZUMA-1, a postmarket registry, as well as other ongoing

		studies with the product
2	Neurotoxicities (identified risk)	<ul style="list-style-type: none"> - Routine PV, REMS, boxed warning in PI, severe adverse events (SAE's) will be followed up on a case-by-case basis - Additional safety information to be derived from long term follow up of clinical trial ZUMA-1, a postmarket registry, as well as other ongoing studies with the product
4	Cytopenias/Febrile Neutropenia (identified risk)	<ul style="list-style-type: none"> - Routine PV - Additional safety information to be derived from long term follow up of clinical trial ZUMA-1, a postmarket registry, as well as other ongoing studies with the product
5	Infection (identified risk)	<ul style="list-style-type: none"> - Routine PV - Additional safety information to be derived from long term follow up of clinical trial ZUMA-1, a postmarket registry, as well as other ongoing studies with the product
6	Secondary malignancy (potential risk)	<ul style="list-style-type: none"> - Routine PV - Additional safety information to be derived from long term follow up of clinical trial ZUMA-1, a postmarket registry, as well as other ongoing studies with the product
7	Generation of RCR (potential risk)	<ul style="list-style-type: none"> - Routine PV, long term follow up study, events will be followed up on a case-by-case basis - Additional safety information to be derived from long term follow up of clinical trial ZUMA-1, a postmarket registry, as well as other ongoing studies with the product
8	Use in Pediatric population (missing information)	<ul style="list-style-type: none"> - Routine PV - The disease for which the product is indicated rarely occurs in children, and the Sponsor indicates that there is low risk of use of the product in pediatric patients; however, a pediatric study involving use of the product for a

		different indication is planned.
9	Use in patients who may be pregnant or nursing (missing information)	- Routine PV - Label states that this therapy is not recommended for this patient population

The sponsor describes “routine pharmacovigilance” as: “collect[ion] and process[ing of] AE reports from multiple sources (spontaneous reporting from healthcare professionals and consumers, regulatory agencies, scientific literature, clinical trials, and post-marketing studies, i.e., registries, safety studies)...All newly acquired safety information will continue to be actively monitored, including regular review and evaluation of data and routine systematic review of published literature, case reports, and both individual case and aggregate safety reviews and analysis...Aggregate reports are prepared and submitted to health authorities as required by regulations. These include periodic safety update reports (PSURs), annual safety reports, and other reports as required. Ad hoc reports may be prepared upon identification of a potential safety issue and/or upon request by health authorities.” This plan is consistent with 21 CFR 600.80.

In addition to routine PV, the sponsor proposes several other elements as part of the PVP. The postmarket registry and the Risk Evaluation and Mitigation Strategy (REMS) will be discussed in section 7 and 8, respectively. The sponsor notes that multiple studies are underway or planned to expand the product indication and suggests that additional safety data can be derived from those studies.

The sponsor plans an extension of ZUMA-1 for long term follow up of the patients enrolled under that protocol. This study will continue under the IND with a primary objective of monitoring for new malignancies, as well as neurological, rheumatological, autoimmune (anti-product antibodies), and hematological disorders. Under the protocol, subjects will undergo testing for development of RCR, lymphocyte subset analysis (until end of year 2), and product persistence. Long term efficacy will be evaluated. Follow up will continue for 15 years after the last patient receives the product. Follow up visits will occur at months 3, 6, 9, 12, 15, 18, 24, 30, 36, 42, 48, 54, 60 and then annually for years 6-15.

7. YESCARTA® Phase IV Registry Post Marketing Requirement

- After reviewing the safety data for this product, there is potential for the serious risk of secondary malignancy due to replication-competent retrovirus or insertional mutagenesis. Although these AEs were not seen during the follow up period, the duration of follow up was too short to fully assess this potential risk. A communication was sent to the sponsor informing them that the agency will require a Post Marketing Requirement (PMR) based on section 505(o)(3)(B)(iii) of FDAAA: “to identify unexpected serious risk(s) when available data indicate the potential for serious risk(s).”
- The PMR will be a Phase IV, multi-center, prospective, observational, non-interventional, post market study. The primary objective of this study will be to characterize the type, frequency, and severity of all secondary malignancies and relapses in patients who receive YESCARTA®. The registry will enroll at least 1,500 patients and follow them for 15 years. For secondary malignancies, fresh tumor specimens will be obtained and sent to Kite Pharma to determine whether the malignancy is product-related.
- Table 2 summarizes this registry-type study as proposed by the sponsor. Negotiations are underway to determine whether enrollment of subjects who receive the product for indications

other than the indication currently proposed will be allowed. Additionally, negotiations to optimize specimen collection and testing in the event of secondary malignancy are ongoing.

Table 2: Post Marketing Study (adapted from draft PMR protocol, submitted September 29, 2017)

Study Title:	PROSPECTIVE, LONG-TERM NON-INTERVENTIONAL COHORT STUDY OF RECIPIENTS OF AXICABTAGENE CILOLEUCEL FOR TREATMENT OF RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMAS
Study Design:	This is a prospective, long-term, non-interventional, cohort study of patients with relapsed/refractory large B-cell lymphomas who have received axicabtagene ciloleucel. Patients may enroll from one week prior or up to 6 months after receiving axicabtagene ciloleucel infusion and will be followed for 15 years.
Primary Objective:	To evaluate the development of secondary hematological malignancies after administration of axicabtagene ciloleucel.
Secondary Objectives:	To determine the rates of overall survival and causes of death after administration of axicabtagene ciloleucel. To evaluate the incidence and severity of cytokine release syndrome, and neurologic toxicities after administration of axicabtagene ciloleucel.
Eligibility Criteria:	Recipients of axicabtagene ciloleucel for the treatment of relapsed/refractory large B-cell lymphoma at participating centers who consent to have data reported to the (b) (4)
Treatment Description:	This is a non-interventional study of patients receiving axicabtagene ciloleucel in the post-marketing setting. No treatment is prescribed by this protocol. Axicabtagene ciloleucel is manufactured from a patient's own T cells, which are obtained via leukapheresis. Patients undergo a lymphodepleting chemotherapy regimen followed by a single infusion of axicabtagene ciloleucel.
Accrual Objective:	The target accrual is 1500 patients, of which 500 will be from ongoing axicabtagene ciloleucel studies.
Accrual Period:	The estimated accrual period is up to 5 years to enroll the targeted sample size.
Study Follow up:	All patients will be followed for 15 years after axicabtagene ciloleucel administration.
Statistical Plans:	The targeted accrual will provide 95% and 82% likelihood of detecting one event of interest if the true rate is 1 in 100 and 1 in 250 over a 15-year period, respectively.
Milestone Dates:	Final Protocol Submission: 12/22/2017 Study Completion: 12/30/2039 Final Report Submission: 12/22/2040

8. Risk Evaluation and Mitigation Strategy (REMS)

- CRS and neurotoxicity are serious adverse events that commonly occurred after patients received YESCARTA®; these AEs contributed to deaths during the clinical trial period. Risk mitigation strategies employed during the trials involved use of tocilizumab with or without

corticosteroids in subjects exhibiting Grade 3 or higher CRS, and use of steroids in subjects exhibiting Grade 3 or higher neurotoxicity, with some patients receiving corticosteroids for treatment of Grade 2 neurotoxicity. Additionally, all subjects were admitted as inpatients for seven days following infusion of the product, enabling early detection and treatment of these AEs.

- Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505 1(a)].
- To ensure that the benefits of YESCARTA® outweigh the risks of cytokine release syndrome (CRS) and neurotoxicity, it was determined that a REMS that includes elements to assure safe use (ETASU) is necessary. During the review of this BLA, it was found that the applicant's proposed risk mitigation strategies for CRS and neurotoxicity, which consisted of boxed warnings as well as a communication plan-based REMS, were not adequate to mitigate these risks.
- The REMS for YESCARTA® will ensure that health care settings that administer YESCARTA® are specially certified and have on-site, immediate access to tocilizumab (ETASU B). Furthermore, the REMS will ensure that those who prescribe, dispense or administer YESCARTA® are trained about the management of CRS and neurotoxicity (ETASU C). Negotiations are underway to determine whether site-certification will mandate admission of patients for seven days following infusion. Site-certification will ensure that patients are provided with information on CRS and neurotoxicity and will inform them of the importance of staying near the hospital for at least 4 weeks after receiving treatment, since many emergency rooms and hospitals are unable to adequately treat CRS due to a lack of available tocilizumab.
- The sponsor will submit REMS assessments to FDA at 6 months, 12 months, and then annually thereafter.

9. Recommended Pharmacovigilance Actions

DE agrees with the pharmacovigilance activities proposed by the sponsor in the PVP with adverse event reporting as required under 21 CFR 600.80. Periodic safety reports should include details of the potential risks and missing information identified in this safety review. In addition, the immediate risks of CRS and neurotoxicity necessitate a REMS, and the longer-term risks of secondary malignancy necessitate a PMR. Negotiations are underway to finalize the details of the REMS and PMR.