U.S. FOOD & DRUG ADMINISTRATION

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

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

Date: July 20, 2020

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To: Graeme Price, PhD
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Subject: Review of Pharmacovigilance Plan

Applicant: Kite Pharma Inc.

Product: Brexucabtagene Autoleucel

Application: STN 125703/0

Proposed Indication: Treatment of Relapsed/Refractory Mantle Cell Lymphoma

Submission Date: December 11, 2019

Action Due Date: August 8, 2020

1 Introduction

1.1 Objective

The applicant is seeking approval to market and distribute the Chimeric Antigen Receptor-T cell (CAR-T) product, brexucabtagene autoleucel (trade name Tecartus) (the product will be referred to in this memo by its name in the original submission: KTE-X19) in the United States. The purpose of this memo is to assess the adequacy of the applicant's submitted pharmacovigilance plan and to identify potential safety issues that may need to be addressed through additional postmarketing studies, or Risk Evaluation and Mitigation Strategy (REMS), should this product be approved. The safety database includes pivotal study ZUMA-2, and an Integrated Safety Set (interim results from ZUMA-3, ZUMA-4, ZUMA-8).

1.2 Product Description

KTE-X19 is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). The applicant's proposed trade name is Tecartus. The product's predecessor, Yescarta (axicabtagene ciloleucel), is also a CD19-directed genetically modified autologous T cell immunotherapy and was approved for the treatment of relapsed or refractory Diffuse Large B cell Lymphoma (DLBCL), primary mediastinal large B cell lymphoma, and DLBCL arising from follicular lymphoma. KTE-X19 shares a vector with Yescarta (axicabtagene ciloleucel) and initially ZUMA-2 involved axicabtagene ciloleucel, however, high circulating blast counts led to manufacturing failures and the X19 process was developed. KTE-X19 is manufactured via a multi-step process. First, the patient's white cells are leukapheresed in the local hospital/infusion center. The white cells are then sent to a Kite manufacturing facility where they are purified including a T cell enrichment step not present in Yescarta. The cells are transduced with the CAR-T gene and (b) (4) to achieve the desired dose. They are then returned to the local hospital/infusion center and given to the patient. Prior to infusion the patient receives lymphodepleting chemotherapy.

1.3 Proposed dosing regimen(s) and formulation(s)

KTE-X19 is a suspension of CAR-T cells in approximately 68 mL and its target dose is 2 $X10^6$ CAR-positive viable T cells per Kg body weight. KTE-X19 is given as a single infusion.

1.4 Pertinent Regulatory History

After development of the modifications of the Yescarta manufacturing process, discussion with FDA and EMA determined that the resulting product would be considered a novel biologic and ZUMA-2 was continued with KTE-X19.

2 Materials Reviewed

The materials reviewed in support of the assessment are listed in the table below.

Table 1: Materials used in course of review

Source	Document
Applicant	Pharmacovigilance plan submitted in 125703/0 on 12/11/2019
Applicant	Draft US Package Insert submitted in 125703/0 on 12/11/2019
Applicant	KT-US-472-5655 registry study protocol submitted in 125703/0 on 12/11/2019

Source	Document
Applicant	Clinical Overview submitted in 125703/0 on 12/11/2019
Applicant	Summary of Clinical Safety submitted in 125703/0 on 12/11/2019
Applicant	Kite Onc REMS program, REMS document, REMS appended materials and REMS supporting document submitted in 125703/0/3 on 1/6/2020
Applicant	120-day safety update submitted in 125703/0/35 on 4/10/2020
Applicant	Response to information request submitted in 125703/40 on 5/1/2020
Applicant	Yescarta and Tecartus REMS Program, REMS appended materials and REMS supporting document submitted in 125703/50, 125703/51, 125703/55

3 Clinical Trial Experience

3.1 Pivotal Trials

3.1.1 Overview

The applicant submitted data on the pivotal trial for efficacy and safety, ZUMA-2. However, the sponsor also included preliminary safety data for three other trials ZUMA-3, ZUMA-4, and ZUMA-8. These are listed in table 2 below. The discussion of safety data in the clinical trials below involves data from both the applicant's initial submission and the 120-day safety update submitted by the applicant.

Table 2: Clinical Trials

Trial Name	N (safety set)	Description
KTE-C19-102 ZUMA-2	105 leukapheresed; 82 treated Cohort 1: 74 leukapheresed; 68 treated Cohort 2: 17 leukapheresed; 14 treated	Phase 2, multicenter, open label study evaluating the safety and efficacy of KTE-X19 in subjects with relapsed/refractory (r/r) mantle cell lymphoma (MCL). Cohort 1 received KTE-X19 at 2 X 10^6 anti-CD19 CAR-T cells per Kg. Cohort 2 received KTE-X19 at 0.5 X 10^6 anti-CD19 CAR-T cells per Kg. Primary Objective: Evaluate efficacy of KTE-X19 Secondary Objective: Evaluate Safety and tolerability of KTE-X19 Safety Endpoints: Summarize adverse events, deaths, and laboratory values with an onset on or after KTE-X19 Infusion. Follow up: Median 12.3 months (range: 7 to 23 months) Median Age: 65 years (range: 38 to 79 years)
KTE-C19-103 ZUMA-3	125 leukapheresed; 100 treated	Phase 1/2, multicenter, open label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r B-precursor Acute Lymphocytic Leukemia (ALL)
KTE-C19-104 ZUMA-4	45 leukapheresed; 34 treated	Phase 1/2, multicenter, open label study evaluating the safety and efficacy of KTE-X19 in pediatric and adolescent subjects with r/r B-precursor ALL and r/r B-cell Non-Hodgkin Lymphoma (NHL) (will be discussed in pediatric section)
KTE-C19-108 ZUMA-8	10 leukapheresed; 9 treated	Phase 1/2, multicenter, open label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r Chronic Lymphocytic Leukemia (CLL)

Of note, ZUMA-2 initially began with Cohort 1 at 2 X 10^6 anti-CD19 CAR-T cells per Kg. Based on interim analysis of 28 Cohort 1 subjects enrolled and followed for 3 months (9 of which received Yescarta and 19 KTE-X19), it was noted they had 3 - 5 fold higher peak expansion of CAR-T cells compared to ZUMA-1. Given the concern for higher AE rates (Neurotoxicity correlated with higher expansion rates) with higher peak expansion, Kite opened Cohort 2 of

ZUMA-2 dosed at 0.5 X 10^6 anti-CD19 CAR-T cells per Kg. However, interim analysis of Cohort 2 subjects showed less robust response which the applicant was concerned could impact efficacy. Further analysis of Cohort 1 subjects demonstrated more favorable response with similar rates of adverse events (AE) so cohort 2 was closed and the remaining subjects enrolled in cohort 1.

3.1.2 Integrated Safety Analysis (ZUMA 2, ZUMA 3, ZUMA 8)

3.1.2.1 Overview

In ZUMA-2 cohorts 1 and 2, all 82 subjects had an AE and 80 (98%) had an AE at least CTCAE (Common Terminology Criteria for Adverse Events) grade three. In ZUMA-2, 56 of 82 (68%) had a serious AE and 6 (7%) had a fatal AE of which in 3 subjects (4%) was related to disease progression. Of the subjects in ZUMA-2 77 of 82 (94%) had any CRS or neurologic toxicity and 30 (37%) had at worst ≥ Grade 3. Per the ZUMA-2 study report, the median potential follow-up time for all subjects dosed in Cohort 1 was 11.6 months (range 1.9 to 32.3 months) and the median follow up in cohort 2 was 16 months (range 13.9 to 18 months). The AE rates in ZUMA-3 and 8 are similar to ZUMA-2 and are listed in the table below (Table 3).

Table 3 Overview of AEs in ZUMA-2, ZUMA-3, ZUMA-8

	ZUMA-2 (N=82)	ZUMA-3 (N=100)	ZUMA-8 (N=9)
Subjects with at least 1 AE	82 (100%)	100 (100%)	9(100%)
Subjects with at least 1 AE ≥ grade 3	80 (98%)	94 (94%)	9 (100%)
Subjects with serious AE	56 (68%)	77 (77%)	6 (67%)
Subjects with Fatal AE	6 (7%)	22 (22%)	0 (0%)
Number of fatal AR due to disease progression	2 (2%)	10 (10%)	0 (0%)
Any CRS	75 (91%)	91 (91%)	6 (67%)
CRS ≥ grade 3	12 (15%)	27 (27%)	0 (0%)
Any Neurotoxicity	56 (68%)	68 (68%)	7 (78%)
Any Neurotoxicity ≥ grade 3	27 (33%)	31 (31%)	1 (11%)

3.1.2.2 Fatal AEs

In ZUMA-2 22 of 82 subjects (27%) died as of the data cutoff, 18 of 68 subjects (26%) in cohort 1 and 4 of 14 subjects (29%) in cohort 2. 18 of 82 subjects died due to disease progression and 3 subjects died due to AEs: including 1 subject who died of infection in the setting of CRS, 1 subject who died of MRSA bacteremia, and 1 subject who died of cardiac arrest in the setting of CRS

In ZUMA-3, 12 of 100 subjects died due to AEs: 1 died of multi organ dysfunction syndrome in the setting of CRS, 8 subjects died due to infection (sepsis in 2 subjects, one subject each with bacteremia, *Escherichia* sepsis, herpes simplex viremia, pneumonia, fungal pneumonia, septic shock), 2 died of cerebrovascular accident, and one subject died of brain herniation and neurotoxicity secondary to KTE-X19. No subjects died due to an AE in ZUMA-8.

3.1.2.3 Identified Risks

Since Cohort 1 of ZUMA-2 was dosed at the proposed dosing regimen for approval of 2 X 10^6 anti-CD19 CAR-T cells per Kg, this cohort was used by the applicant as the study group to evaluate rates of AEs.

Table 4. ZUMA-2 Overview of Identified Risks

Syndrome (N=68)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
CRS symptoms	62 (91%)	20 (29%)	32 (47%)	8 (12%)	2 (3%)	0 (0%)
Neurotoxicity symptoms	43 (63%)	13 (19%)	9 (13%)	15 (22%)	6 (9%)	0 (0%)
Thrombocytopenia	50 (74%)	8 (12%)	6 (9%)	11 (16%)	25 (37%)	0 (0%)
Neutropenia	59 (87%)	0 (0%)	1 (1%)	10 (15%)	48 (71%)	0 (0%)
Anemia	47 (69%)	0 (0%)	11 (16%)	36 (53%)	0 (0%)	0 (0%)
Infections and infestations SOC	38 (56%)	0(0%)	15 (22%)	18 (26%)	4 (6%)	1 (1%)
Bacterial	10 (15%)	0 (0%)	5 (7%)	4 (6%)	0 (0%)	1 (1%)
Viral	11 (16%)	2 (3%)	7 (10%)	2 (3%)	0 (0%)	0 (0%)
Opportunistic infection	8 (12%)	3 (4%)	5 (7%)	0 (0%)	0 (0%)	0 (0%)
Nonspecific organism, site known	30 (44%)	0 (0%)	11 (16%)	14 (21%)	5 (7%)	0 (0%)
Hypogammaglobulinemia	13 (19%)	1 (1%)	11 (16%)	1 (1%)	0 (0%)	0 (0%)

Table 5. ZUMA-3 and ZUMA-8 Identified Risks

Syndrome	ZUMA-3 (N=100)			ZUMA-8 (N=9)		
	Any Grade	≥ Grade 3	Grade 5	Any Grade	≥ Grade 3	Grade 5
CRS symptoms	91 (91%)	27 (27%)	1 (1%)	6 (67%)	0 (0%)	0 (0%)
Neurotoxicity symptoms	68 (68%)	31 (31%)	1 (1%)	7 (78%)	1 (1%)	0 (0%)
Thrombocytopenia	37 (37%)	34 (34%)	0 (0%)	4 (44%)	3 (33%)	0 (0%)
Neutropenia	52 (52%)	51 (51%)	0 (0%)	8(89%)	8 (89%)	0 (0%)
Anemia	39 (39%)	35 (35%)	0 (0%)	4(44%)	3 (33%)	0 (0%)
Infections and Infestations SOC	39 (39%)	27 (27%)	8 (8%)	2 (22%)	0 (0%)	0 (0%)
Hypogammaglobulinemia	6 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

3.1.2.4 Cytokine Release Syndrome

In ZUMA-2, 62 of 68 subjects (91%) had CRS; 10 subjects (15%) having grade 3 or above. No subjects died of CRS in ZUMA-2. In the supplementary trial results submitted, ZUMA-3 had 28 of 100 subjects (28%) with grade 3 and above CRS.

3.1.2.5 Neurotoxicity Symptoms

In ZUMA-2, 43 of 68 subjects (63%) had documented neurotoxicity, and 21 subjects (31%) had neurotoxicity ≥grade 3. The number of subjects with ≥grade 3 neurotoxicity (21 of 68 [31%]) was higher than those with ≥grade 3 CRS (10 of 68 [15%]) in ZUMA-2, which mirrored the pattern of ≥grade 3 neurotoxicity (35 of 108 [32%]) and CRS (12 of 108 subjects [11%]) reported in ZUMA-1[2]. This was also similar in the ISS trials submitted by the applicant as 32 of 100 (32%) subjects had grade 3 or higher neurotoxicity in ZUMA-3. There were no grade 5 neurotoxicity events in ZUMA-2, but in ZUMA-3 one subject died of cerebral edema and neurotoxicity.

3.1.2.6 Cytopenias

In ZUMA-2, 50 of 68 subjects (74%) had thrombocytopenia, 59 of 68 subjects (87% had neutropenia, and 47 of 68 subjects (69%) had anemia. The rate of those with grade 3 and above was 36 subjects (53%) with thrombocytopenia, 59 subjects (87%) with neutropenia, and 36 subjects (53%) with anemia. In ZUMA-3 and ZUMA-8, at least 37% and 44% of subjects

had some grade of thrombocytopenia, neutropenia, and anemia respectively. However, in all studies there were no deaths attributed to cytopenias.

3.1.2.7 Infection

In the ZUMA-2 trial 38 of 68 subjects (56%) had an event under the infections and infestations SOC and 23 (34%) had a ≥ grade 3 with one subject having a fatal event due to KTE-X19 (see above). Of the 28 of 68 reports (42%) with a known organism, bacterial and viral infections were seen in 10 subjects each (15%) Opportunistic infections occurred in 8 of 68 subjects (12%) with no events assessed as ≥ grade 3 severity. Infections were also reported in ZUMA-3, with 39 of 100 subjects (39%) experiencing ≥grade 3 severity events and 8 of 100 subjects (8%) having fatal infections.

3.1.2.8 Hypogammaglobulinemia

Hypogammaglobulinemia occurred in 13 of 68 subjects (19%) with 1 subject (1%) experiencing grade 3 hypogammaglobulinemia. There were no fatal events of hypogammaglobulinemia in ZUMA-2.

3.1.3 Important Potential Risks noted in ZUMA-2 trial – Secondary Malignancy and Tumor Lysis Syndrome

Regarding secondary malignancy in the ZUMA-2 trial, 7 of 68 subjects had events within SOC of neoplasms benign, malignant, and unspecified. Of the 7 subjects, none appeared to have developed a malignancy secondary to treatment with KTE-X19. Subjects were tested for immunogenicity and replication competent retrovirus (RCR) in the ZUMA-2 trial and no subjects tested positive on complete testing for either antibodies to the CAR construct or RCR.

One subject in ZUMA-2 had grade 3 tumor lysis syndrome which appears to be related to KTE-X19 and occurred on day 2 to day 14.

3.1.4 Missing Information in ZUMA-2 trial

There were no pregnant or lactating women enrolled in the ZUMA-2 or associated trials ZUMA-3, ZUMA-4, ZUMA-8. Therefore, there is no information on use of KTE-X19 in pregnant women.

One subject in ZUMA-2 developed an autoimmune disease - autoimmune colitis that occurred on day 348 and was deemed serious by the reporter.

3.1.5 Pediatric Study

The only study enrolling pediatric patients is ZUMA-4 (34 subjects dosed at time of data cutoff). In ZUMA-4 32 subjects were less than 18-years-old, one subject was 18 years of age, and one subject was 20 years old. As of data cutoff 34 subjects had been enrolled and treated with KTE-X19. Regarding AEs in the population, all 34 subjects had one AE and 33 (97%) had ≥ Grade 3 AE. Of the 34 subjects, 24 (71%) had a SAE, 20 (59%) had a SAE related to KTE-X19. In the study 11 (32%) subjects died: 8 (23%) due to disease progression, one due to GvHD post allo-SCT, and 2 (7%) had fatal AEs, one was due to mucormycosis and one due to *Escherichia* sepsis.

Table 6. ZUMA-4 Identified Risks

Syndrome (N=34)	Any Grade	≥ Grade 3	Grade 5
CRS symptoms	30 (88%)	8 (24%)	0 (0%)
Neurotoxicity symptoms	22 (65%)	9 (26%)	0 (0%)
Thrombocytopenia	11 (32%)	10 (29%)	0 (0%)
Neutropenia	13 (38%)	13 (38%)	0 (0%)
Anemia	16 (47%)	16 (47%)	0 (0%)
Infections and Infestations SOC	17 (50%)	11 (32%)	1 (3%)
Hypogammaglobulinemia	6 (18%)	0 (0%)	0 (0%)

3.1.5.1 Identified Risks

Cytokine Release Syndrome symptoms were noted in 30 of 34 subjects (88%) with ≥grade 3 in 8 (24%). Neurotoxicity symptoms were noted in 22 of 34 subjects (65%) with ≥grade 3 in 9 (26%). There were no fatal CRS and neurotoxicity events in the ZUMA-4 subjects. The number of patients with ≥ grade 3 cytopenias was 11 of 34 subjects (32%) with thrombocytopenia, 13 subjects (38%) with neutropenia and 16 subjects (47%) with anemia. The number of subjects with infections in ZUMA-4 was 17 (50%) with 11 (32%) ≥grade 3 and 1 (3%) grade 5 (fatal).

3.1.5.2 Potential Risks and Missing Information

In ZUMA-4 there were 2 cases of secondary malignancies. Both were cases of acute lymphoblastic leukemia, and were determined to be related to the underlying malignancy. In ZUMA-4 no subject had experienced tumor lysis syndrome. One subject in ZUMA-4 had a grade 1 Graft vs Host Disease (GvHD) event that was not serious.

4 Post Marketing Data

4.1 Database Query

On March 5, 2020, FAERS was queried with the verbatim product name “KTE-X19” and no limits on dates or severity. This search disclosed 4 cases, of which all were enrolled in clinical trials (2 of ZUMA-2, 1 of ZUMA-3 and ZUMA-4).

5 Pharmacovigilance plan

5.1 Safety Issues

Safety issues identified by the applicant as well as the applicant’s proposed risk mitigation strategies were reviewed from the submitted pharmacovigilance plan (PVP), version 1.0, dated December 5, 2019, in 125703/0. These plans are summarized in the table below adapted from 3.2.1 in the PVP.

Table 7: KTE-X19 Sponsor-Proposed Pharmacovigilance plan

Safety Concerns	Planned Action
Important identified risks	
• Serious Neurologic Events including cerebral edema • Cytokine Release Syndrome (CRS)	■ Routine Pharmacovigilance including follow up questionnaire for Adverse Event Reports submitted to Applicant ■ Expedited reporting of cases of Grade 4 or worse ICANS or CRS ■ Registry study to monitor the occurrence of symptoms in the postmarket setting

Safety Concerns	Planned Action
	■ Adverse event reporting through proposed REMS ■ Additional information from clinical studies using KTE-X19
• Cytopenias • Infections • Hypogammaglobulinemia	■ Routine PV ■ Registry study to monitor the occurrence of symptoms in the postmarket setting ■ Additional information from clinical studies using KTE-X19
Important potential risks	
• Secondary Malignancy	■ Routine PV ■ Registry study to monitor the occurrence of symptoms in the postmarket setting ■ Additional information from clinical studies using KTE-X19
• Immunogenicity	■ Conducting Assessments of antibody formation in clinical studies using KTE-X19
• Generation of Replication competent retrovirus	■ Conducting Assessments for RCR in clinical studies using KTE-X19 ■ Registry study to monitor the occurrence of events in the postmarket setting
• Tumor Lysis Syndrome • Aggravation of Graft Versus Host Disease (GvHD)	■ Routine PV ■ Additional information from clinical studies using KTE-X19
Important missing information	
• Use in Pregnancy and Lactation	■ Routine PV ■ Registry study to monitor AE reports in Pregnant and Lactating patients treated with KTE-X19 in the postmarket setting
• New occurrence or exacerbation of autoimmune disorders	■ Routine PV
• Long Term Safety	■ Routine PV ■ Registry study to evaluate prolonged or delayed AEs in the postmarket setting ■ Additional information from clinical studies using KTE-X19

5.2 Planned pharmacovigilance activities

The applicant proposes several routine pharmacovigilance activities. Per the applicant: "*Gilead will collect and process AE reports from multiple sources and store in a centralized and validated company safety database. Kite will perform medical reviews to identify important single cases of potential safety signals and conduct appropriate follow up*." Additionally, the applicant will use targeted questionnaires to collect specific data in reports containing the AEs CRS or ICANS. The applicant also reports submitting aggregate reports to health authorities (PBRERS/PSURs) and additional ad hoc reports involving a safety issue. This plan is consistent with 21 CFR 600.80.

The applicant also proposes two additional PV actions, a combined Yescarta and KTE-X19 REMS, and an observational postmarketing registry study, which are detailed below. The sponsor also notes that multiple studies are underway to expand the product indication (preliminary reports of several studies were reported in the Integrated Safety Set) and suggests that additional safety data can be derived from those studies. These indications will be separately reviewed when the sponsor seeks to broaden the indicated uses for KTE-X19 via efficacy supplement.

5.2.1 Yescarta and Tecartus Risk Evaluation and Mitigation Strategy

The applicant proposes a REMS to mitigate the serious known risks of cytokine release syndrome and neurotoxicity noted in the ZUMA-2 trial. The risk mitigation strategies involve recognition and early treatment of CRS with tocilizumab and steroids and treatment of neurotoxicity with steroids. These strategies have been shown to reduce the severity of CRS and ICANS[1]. These risk mitigation strategies have been implemented in the clinical trial setting for KTE-X19 and similar CAR-T products as well as in the postmarketing setting, under approved REMS programs, for marketed CAR-T products, Kymriah and Yescarta. Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes the FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the FDA determines that such a strategy is necessary to ensure the benefits of the drug outweigh the risks. The applicant's proposed REMS has the following goals:

1. Ensuring that hospitals and their associated clinics that dispense a Kite Chimeric Antigen Receptor (CAR) T-cell therapy are specially certified and have on-site, immediate access to tocilizumab.
2. Ensuring those who prescribe, dispense, or administer a Kite CAR T therapy are aware of how to manage the risks of CRS and neurological toxicities.

The applicant is proposing inclusion of two products, KTE-X19 and Yescarta, consolidated into a single newly established REMS, *The Yescarta [axicabtagene ciloleucel] and Tecartus [brexucabtagene autoleucel] REMS program.* Yescarta, also a CD19-directed genetically modified autologous T cell immunotherapy with similar serious risks and manufactured by the same applicant, was previously approved in 2017, with a REMS to mitigate the serious risks of cytokine release syndrome (CRS) and neurological toxicities. The applicant is proposing merging the extant Yescarta REMS into the combined Yescarta and Tecartus REMS given the similar risks, and the same risk mitigation measures with identical goals of the REMS with elements to assure safe use (ETASU) and REMS requirements for both KTE-X19 and Yescarta. [Note that to transition the extant Yescarta REMS into the combined Yescarta and Tecartus REMS Program, the applicant has submitted a REMS major modification for Yescarta under STN 125643/233 for FDA review.] As part of the plan for the proposed combined REMS, the applicant provided a transition plan. In the proposed plan, those certified hospitals in the Yescarta REMS would apply to the Yescarta and Tecartus REMS. The hospital's authorized representative would then use the hospital enrollment form to re-enroll, and they and the healthcare providers (HCP)s at the site would take the training and knowledge assessment.

As with the previous Yescarta REMS, to achieve the goals of the newly proposed combined REMS that will include Tecartus and Yescarta, the applicant plans to certify hospitals and their associated clinics and enroll hospitals into the program. The REMS program will require sites to have on-site, immediate (within 2 hours) access to tocilizumab and healthcare provider training about the management of CRS and neurotoxicity. They have also proposed a REMS assessment plan to ensure there is regular evaluation of whether the REMS is meeting its goals. The applicant proposes to submit REMS assessments at 6 months, 12 months, and annually thereafter. The REMS assessment submissions will contain information on:

- Hospital and their associated clinic enrollment and education statistics
- Utilization by Kite CAR-T product
- Compliance with the combined REMS

- Combined REMS customer care center
- An evaluation of the understanding of risks and mitigation strategies of the REMS
- An assessment to which the approved strategy is meeting the goal of the REMS

5.2.1.1 DE Review of Applicant's Proposed REMS Program

DE review of the proposed REMS program incorporated input from CDER Division of Risk Management (DRM) and the Office of the Chief Counsel (OCC). DE presented the combined REMS program for Yescarta and Tecartus to the CBER Safety Working Group (SWG) on May 28, 2020. It was determined that a REMS that includes ETASU is necessary to ensure that the benefits of Tecartus outweigh the risks of CRS and neurotoxicity, and that the applicant's proposal for a combined REMS Program for Yescarta and Tecartus was acceptable and would minimize the burden on the healthcare delivery system by allowing both products to be dispensed under one REMS program with shared REMS requirements for both products. The combined REMS program will ensure that health care settings that administer Yescarta and/or Tecartus are specially certified and have on-site, immediate access to tocilizumab, and ensure that those who prescribe, dispense or administer these products are trained about the management of CRS and neurotoxicity. During the review of this BLA, it was found that the applicant's proposed REMS program was adequate to mitigate these risks, after incorporation of additional FDA recommendations discussed below.

The applicant's initial proposed name for the combined REMS, the KITE ONC REMS, was determined to be inconsistent with naming conventions for existing REMS programs . The term KITE ONC is too broad as the proposed REMS does not cover all oncology products. After discussion with the Division of Risk Management (DRM/CDER) and in order to align the name of the Tecartus/Yescarta REMS with other extant combined REMS (for example, the "Suboxone and Subutex REMS Program"), we recommended that the combined REMS program be named "*The Yescarta [axicabtagene ciloleucel] and Tecartus [brexucabtagene autoleucel] REMS program* ."

Additional changes to the proposed REMS recommended to improve the effectiveness of the combined Yescarta and Tecartus REMS are listed below:

1. Questions specifically referencing the approved and proposed indications for Yescarta and Tecartus respectively were removed from the REMS assessment. The applicant has reported multiple trials currently underway involving both Yescarta and Tecartus to expand the approved indications. As specific knowledge of indication is not necessary to achieve the goals of the REMS, it is reasonable to remove these questions from the knowledge assessment.
2. The combined REMS will include implementation of an online Learning Management System (LMS) for knowledge assessments. The REMS Document was modified to include language to make the online LMS accessible from the REMS website: "*The REMS Program website must include the capability to complete training online, maintain records of that training…"* The applicant agreed to include a hyperlink on the REMS website to access the LMS.
3. The REMS Document was modified to include the following requirement for the applicant, "*Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS program*." This was recommended to align the language with standard templated text as per the FDA Guidance on the *Format and Content of a REMS Document* (2017) as well as with language in an existing REMS

program for a different CAR-T, Kymriah REMS. This is also consistent with the applicant's online Learning Management System (LMS). The applicant agreed to maintain a central online database that includes all knowledge assessment data, including knowledge assessments completed in the online LMS as well as data entered from knowledge assessments completed on paper and emailed/faxed to the applicant, or collected during onsite audits. The central online database will ensure that the results of knowledge assessment completion will be retained and improve compliance with REMS assessment metrics.

4. The language in the REMS Document regarding "first order audits" was modified from "*audit hospitals within 180 days of product delivery*" to "*audit hospitals within 180 days of first order*" to align with language in approved REMS programs for Yescarta and Kymriah. The applicant had previously changed the information in the supporting document to increase the amount of time until the first order audit is required. We recommended that the applicant continue to audit hospitals within 180 days of first order because the REMS Program requirements need to be in place at certified sites prior to placement of first order, regardless of when the product is actually delivered to the sites.

5.2.2 Long term follow up postmarketing study

There is potential for the serious risk of secondary malignancy due to replication-competent retrovirus or insertional mutagenesis associated with this product (please see section 6.2 for further discussion). Although these AEs were not seen during the clinical trials, the duration of follow up was too short to fully assess this potential risk in the premarket setting and requires further assessment by collecting safety data in a postmarket study.

5.2.2.1 Sentinel Sufficiency Assessment

As required by regulations under section 901 of Food and Drug Administration Amendments Act (FDAAA) and as described in the *CBER SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments*, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e. capability) of the CBER Sentinel program to further characterize the serious risk of secondary malignancy associated with KTE-X19. Please see attached Sentinel sufficiency memorandum, which concludes that the CBER Sentinel program is not sufficient to assess the serious risk of secondary malignancies because data sources are:

- unable to identify the specific brand KTE-X19 using CPT and ICD 10 billing codes
- unable to identify outcomes with a long (15 years) follow up period
- unable to collect tumor tissue needed for testing for persistence of the vector used in KTE-X19

Sentinel insufficiency serves as a justification for whether a safety-related postmarketing requirement study is warranted under Section 901, Title IX of FDAAA. Therefore, the applicant will be required to conduct a postmarketing study to further assess secondary malignancies and long-term safety as a postmarketing requirement (PMR) (see section 5.2.2.2).

5.2.2.2 Postmarketing requirement (PMR): KT-US-472-5655 Long Term Registry study with KTE-X19

In the review of ZUMA-2, the median follow up period for cohort 1 was 16.8 months (range 7.2 to 37.6 months). As there are only 2 other approved CAR-T products in the US, Yescarta and

Kymriah (both approved in 2017), the long-term safety of CAR-T products is unknown. To further evaluate the safety of these products and monitor for secondary malignancies, both Yescarta and Kymriah have ongoing long term safety monitoring studies. As KTE-X19 shares similar risks of long-term toxicities, especially related to replication competent retrovirus and insertional mutagenesis, the applicant has proposed a registry post marketing study which will be a postmarketing requirement (PMR) safety study under Section 505(o) of the Federal Food, Drug, and Cosmetic Act.

Table 8: Study synopsis of KT-US-472-5655

Study Title	Prospective Long-term Noninterventional Cohort Study of Recipients of KTE-X19 for Treatment of Relapsed or Refractory Mantle Cell Lymphoma
Study Design	Study is a prospective, long term, noninterventional cohort study of patients with (r/r) Mantle Cell Lymphoma (MCL) that have received KTE-X19. Patients receiving KTE-X19 enrolled and followed 15 years.
Primary Objective	To evaluate the development of subsequent neoplasms after administration of KTE-X19
Secondary Objective	The following events will be determined/evaluated after KTE-X19 • Overall survival • Causes of Death • Rate of relapse of primary malignancy • Time to relapse or progression of the primary disease • Incidence and severity of cytokine release syndrome, neurologic toxicities, serious infections, prolonged cytopenias, and hypogammaglobulinemia • Pregnancy outcomes in females of childbearing potential • Duration of response (DOR) time from date of first documented response (CR or partial response [PR]) to date of first document progression, or first document relapse, or death due to primary disease, which ever happens first
Eligibility Criteria	Recipients of KTE-X19 for r/r MCL at centers who consent to have data reported to Center for International Blood and Marrow Transplant Research (CIBMTR)
Treatment Description	No treatment is proposed in the noninterventional protocol.
Accrual Objective	The sponsor's amended proposed target accrual is 500 patients
Accrual Period	The sponsor's proposed period to reach target accrual is 5 years
Study Follow Up	Subjects will be followed for 15 years after KTE-X19
Statistical Plans	Per sponsor target accrual will be able to detect event of interest at: 99% likelihood if true rate 1:50 91% likelihood if true rate 1:100 80% likelihood if true rate 1:150 71% likelihood if true rate 1:200 62% likelihood if true rate 1:250
Milestone Dates	Final protocol Submission: 3 months after Biologics License Application approval Study Completion: 20 years after protocol approval Final report submission: 1 year after study completion

Evaluation of the development of secondary malignancy will require the collection of tumor tissue and analysis by (b) (4) for γ-retroviral vector and replication competent retrovirus. The applicant will also perform insertional mapping if T-cell malignancy is suspected. The applicant's initial proposed target accrual was 350 subjects over five years. As this target was too low, the FDA asked the applicant to increase target accrual and to provide a justification of the sample size. In response to the FDA's request, the applicant agreed to increase target accrual to 500 subjects over 5 years. Their rationale is that ~200 patients could receive KTE-X19 yearly and 100 subjects a year (for a total of 500) would represent 50% recruitment of eligible patients.

DE presented the above study to the SWG on May 28, 2020, and the SWG concurred with the plan for this proposed PMR.

6 Integrated Risk Assessment

6.1 Identified Risks

6.1.1 CRS and Neurotoxicity

The applicant has several proposals to mitigate the identified risks of CRS and Neurotoxicity, including a boxed warning in the proposed label, and the REMS Program. These risks are known AEs of Yescarta[2] seen in clinical trials and also noted in the ZUMA-2 trial with KTE-X19. There is evidence that these risks are potentially serious, given that 15% of CRS and 31% of Neurotoxicity events were ≥grade 3 severity, though no events were fatal in ZUMA-2. The underlying cause of CRS is thought to be due to release of inflammatory cytokines from infused CAR-T and other immune cells[3]. However, the underlying cause of neurotoxicity is less well understood, and its clinical presentation can vary widely[4]. Nonetheless, both syndromes are clearly associated with CAR-T use in general and based on reports of ZUMA-2 with KTE-X19 in particular. The first proposed risk mitigation activity is the sponsor's proposed REMS, which has the explicit goals of training providers to recognize CRS and Neurotoxicity as well as ensuring that hospitals have tocilizumab (an IL-6 receptor antagonist used to treat CRS) available for patients. In addition, the registry study proposed by the applicant has as a secondary endpoint tracking the incidence and severity of CRS and Neurotoxicity as well as all-cause mortality. The applicant will report life threatening or fatal CRS and neurotoxicity as expedited reports, ensuring timely assessment of these AEs of interest. In addition, the applicant plans to send AE follow up forms to those providers that report CRS or neurotoxicity to ensure complete information about the case is shared with the applicant. The applicant's PV plan with regard to the identified risks of CRS and neurotoxicity is reasonable.

6.1.2 Cytopenias

Cytopenias (thrombocytopenia, anemia, neutropenia) were noted in a majority of patients in the ZUMA-2 trial, and a majority had ≥ Grade 3 anemia and neutropenia. In patients receiving Tecartus, lymphodepleting chemotherapy prior to infusion of KTE-X19 likely contributed to the cytopenias[3]. These cytopenic events can persist for a significant amount of time after CAR-T infusion, and have been documented as lasting up to 21 months[5]. The applicant's risk mitigation plan includes routine PV to monitor cytopenias as well as employing the registry study to record the incidence and severity of cytopenias in patients enrolled in the study. As most of these AEs are likely related to the conditioning chemotherapy as opposed to KTE-X19, this is reasonable.

6.1.3 Infections

In ZUMA-2 a majority (56%) of subjects developed infections and 32% had ≥ grade 3 infections. In addition, two subjects died of infections after infusion of KTE-X19. In a study of long term effects of CAR-T products, a significant majority (61%) had an infection with 5% needing intensive care[5]. In the long term follow up of the ZUMA-1 trial involving Yescarta, 30 subjects (28%) developed ≥ grade 3 infections and no subjects in ZUMA-1 had fatal infections[2]. Patients receiving CAR-T products in general and KTE-X19 in particular have multiple risk factors for infection: the conditioning chemotherapy, immunosuppression due to B cell depletion due to anti-CD19 CAR-T, use of tocilizumab or steroids treating CRS or neurotoxicity, and immunosuppression by the malignancy itself[3]. Therefore, it is difficult to attribute all infections seen in the post infusion period to receipt of KTE-X19. Other than routine pharmacovigilance the applicant plans to use the registry study to monitor the incidence and severity of infections.

6.1.4 Hypogammaglobulinemia

Hypogammaglobulinemia is a known and expected adverse event with anti-CD19 CAR-T therapy and represents an on-target off-tumor adverse event[5]. There were no fatal events and only 20% of patients had any grade hypogammaglobulinemia with KTE-X19. The sponsor's plan is to monitor this identified risk through routine pharmacovigilance as well as assessing events of hypogammaglobulinemia through the registry study.

6.2 Potential Risks

6.2.1 Secondary Malignancy and Replication Competent Retrovirus

There are two possible adverse events related to the CAR-T manufacturing process, secondary malignancy and replication competent retrovirus. Secondary malignancies can occur due to insertional mutagenesis of the CAR construct, though patients receiving CAR-T therapy have multiple additional risk factors for secondary malignancy, including older age and prior chemotherapy. In one single center review, 13 of 86 patients (15%) had a subsequent malignancy including 6 (7%) with non melanoma skin cancer (median time to onset 16 months), 4 with (5%) myelodysplastic syndrome (median time to onset 6 months), 1(1%) with melanoma (diagnosed at 8 months), 1(1%) with noninvasive bladder cancer (diagnosed at 2 months), and 1 (1%) with multiple myeloma (diagnosed at 6 months)[5]. Additionally another observational study demonstrated that the risk of subsequent malignancies remains above baseline several years post conventional treatment of DLBCL compared to the general population[6]. Given that the median follow up for subjects in Zuma 2 was 11.6 months, risk of secondary malignancy following treatment with Tecartus has been insufficiently characterized thus far. The applicant is proposing a registry study to follow patients with the primary endpoint to evaluate for subsequent neoplasms, and this study will be a postmarketing requirement (see section 5.2.2). Per the proposal, "*Patients who develop a subsequent neoplasm and provided informed consent will be requested to provide blood for assay of the presence of γ-retroviral vector sequences and RCR as indicated*." The PMR study and routine pharmacovigilance, will provide adequate monitoring for this risk.

6.3 Missing Information

6.3.1 Pregnant Women

Pregnant women were excluded from the trials with KTE-X19. The safety of this product is not known in women who are pregnant. The sponsor proposes to monitor pregnancy outcomes in

this patient population as part of the registry study. This is reasonable and these patients will also be followed by routine pharmacovigilance.

7 Recommended Pharmacovigilance Actions

Should Tecartus be approved, DE agrees with the pharmacovigilance activities proposed by the sponsor in the PVP (version 1.0, dated December 5, 2019) 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 serious risks of CRS and neurotoxicity will require an ETASU REMS to ensure that the benefits of the drug outweigh the risks. The REMS program will require hospital sites to be specially certified and have on-site, immediate (within 2 hours) access to tocilizumab and healthcare provider training about the management of CRS and neurotoxicity. The Yescarta REMS will be consolidated into a shared system, the Yescarta and Tecartus REMS, to decrease overall burden on the healthcare system. The REMS Document and appended materials are under review; please see the final version of the REMS Document and REMS Materials submitted by the applicant for the agreed-upon elements of the Tecartus REMS. A PMR safety study will be required to assess a serious risk of secondary malignancies and long-term safety of Tecartus. Negotiations are underway to finalize the details of the REMS and PMR.

8 References

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