Summary Basis for Regulatory Action

Date: 23rd July 2020

From: Graeme Price PhD, Chair of the Review Committee

BLA STN#: 125703

Applicant Name: Kite Pharma, Inc.

Date of Submission: 11th December 2019

Goal Date: 11th August 2020

Proprietary Name/ Established Name: TECARTUS/brexucabtagene autoleucel

Indication: Relapsed/refractory Mantle Cell Lymphoma

Recommended Action:
The Review Committee recommends accelerated approval of this product.

Review Office(s) 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.**

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

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Graeme Price, PhD (OTAT/DCGT) Jakob Reiser, PhD (OTAT/DCGT) Tal Salz, PhD (OTAT/DCGT) Donald Ertel (OCBQ/DMPQ) Simleen Kaur (OCBQ/DBSQC) Marie Anderson, PhD (OCBQ/DBSQC)
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Megan Zimmerman, MD (OTAT/DCEPT) Helkha Peredo-Pinto, MD MPH (OTAT/DCEPT) Christopher Jason, MD (OBE) Bhanumathi Kannan (OCBQ/BIMO)
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Xue Lin, PhD (OBE)
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Gaya Hettiarachchi (OTAT/DCEPT)
Clinical Pharmacology Review(s)	Xiaofei Wang, PhD (OTAT/DCEPT)
Labeling Review(s) • *APLB (OCBQ/APLB)*	Dana Jones (OCBQ/APLB)
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	
Advisory Committee summary	No advisory committee meeting was held

1. INTRODUCTION

Kite Pharma, Inc., submitted a Biologics License Application (BLA), STN 125703, for licensure of brexucabtagene autoleucel. Brexucabtagene autoleucel, with the proprietary name of TECARTUS, is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory Mantle Cell Lymphoma (r/r MCL).

TECARTUS is comprised of genetically modified, antigen-specific autologous T cells reprogrammed to target cells that express CD19, an antigen expressed on the surface of healthy and malignant B cells. The TECARTUS chimeric antigen receptor (CAR) protein has a murine single chain variable fragment (scFv) specific to human CD19 linked to two signaling domains derived from human CD28 and CD3ζ. The CAR protein plays a critical

role in TECARTUS function, mediating T cell activation and anti-tumor effector function following binding of the scFv to CD19. The CAR expressed in TECARTUS is identical to that in YESCARTA (axicabtagene ciloleucel), a CD19-directed genetically modified autologous T cell immunotherapy approved in 2017 for relapsed or refractory large B cell lymphoma. TECARTUS differs from YESCARTA in that T cells are enriched during the TECARTUS manufacturing process; T cell enrichment is not performed during YESCARTA manufacture.

This document summarizes the basis for approval of TECARTUS. A single clinical trial, ZUMA-2, provides the primary evidence of safety and effectiveness for the BLA submission. The recommendation for accelerated approval is based on the objective response rate (ORR) and preliminary duration of response demonstrated in the study. The major risks of TECARTUS include cytokine release syndrome (CRS) and neurologic toxicity, either of which can be life-threatening, as well as infections and prolonged cytopenias.

The clinical review team recommends accelerated approval of this BLA with postmarketing requirements (PMRs) for:

1. A Risk Evaluation and Management Strategy (REMS) with Elements to Assure Safe Use (ETASU) for the management of CRS and neurological toxicity, and a postmarketing observational study to primarily assess long-term toxicities of TECARTUS.
2. Additional follow-up of subjects enrolled in ZUMA-2's Cohort 1 to a minimum of 18 months from the time of first objective response to assess durability of response.
3. A study of TECARTUS in subjects who have not been exposed to a Bruton tyrosine kinase (BTK) inhibitor to confirm clinical benefit in patients with relapsed or refractory mantle cell lymphoma regardless of prior treatment with available products.

The recommendation for accelerated approval is being made after consideration of the following:

1. Available therapies for patients with r/r MCL. Products with traditional FDA approval have objective response rates (ORRs) of 31% and complete response (CR) rates of 8% at best, while the BTK inhibitors under accelerated approval have ORRs up to 84%, CR rates as high as 50%, and a median duration of response as long as 19.5 months.
2. Published data on patients relapsed after or refractory to BTK inhibitors following prior therapy which included bendamustine and/or an anthracycline. Data are limited and prone to bias.
3. The magnitude of benefit observed in ZUMA-2 as illustrated by ORR and CR rate, understanding that disease responses were likely more difficult to achieve in the study population than in the broader r/r MCL population.
4. TECARTUS' mechanism of action is via CD19 targeting and T cell-mediated cell death. BTK inhibition is mediated via its effect on a non-receptor tyrosine kinase and therefore represents a different mechanism of tumor toxicity from CD19 targeting. Thus, prior BTK inhibitor therapy is unlikely to have enhanced CD19 expression or enhanced CD19-mediated CAR T cell-mediated tumor cell killing in patients who were relapsed or refractory to BTK inhibition. It is therefore biologically plausible that the tumoricidal activity of CD19-directed CAR T cell therapy is likely to be similar in BTK inhibitor-naïve and BTK-refractory or relapsed patients.

2. BACKGROUND

Disease Background

Mantle cell lymphoma (MCL), comprising roughly 6% of non-Hodgkin lymphomas, is an aggressive malignancy arising from antigen-naïve pre-germinal center B cells found in lymph nodes' mantle zone. As a B cell disorder, MCL expresses the surface antigens CD19 and CD20. The disease is further characterized by overexpression of the cell cycle regulator cyclin D1, driven by MCL's distinguishing t(11;14)(q13;q32) chromosomal translocation. The annual incidence of MCL is about one to two cases per 100,000 Americans, predominantly Caucasians. Median age at diagnosis is 68 years. Men develop MCL approximately three times more frequently than women. The most well-established prognostic indicators at the time of diagnosis are pleomorphic or blastoid histology, which predict worse outcomes, and the MCL International Prognostic Index (MIPI) score, which considers patients' performance status, age, lactate dehydrogenase (LDH) level, and white blood cell (WBC) count to identify low-, intermediate-, and high-risk groups. No validated prognostic factors have been identified in the relapsed or refractory setting. Although nearly all patients respond at least partially to frontline therapy, relapse is the rule. Prognosis progressively worsens with each relapse, and most patients ultimately die from disease progression.

Available therapies

Although first-line treatment of MCL typically consists of combination chemotherapy in conjunction with an anti-CD20 monoclonal antibody, subsequent therapies vary widely depending upon patient age, fitness, and comorbidities, as well as physician discretion and patient preference. There is no consensus or clear guidance on the optimal approach. Bendamustine plus rituximab is perhaps the most commonly utilized treatment in relapsed or refractory (r/r) disease and has demonstrated objective response rates (ORRs) ranging from 71% to 92%, with complete response rates of 38% to 50%. Other options range from monotherapy with agents like rituximab or cladribine to complex regimens such as rituximab, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab, high-dose methotrexate, and cytarabine. For a minority of candidates with adequate health and chemosensitive disease, autologous or allogeneic hematopoietic stem cell transplantation (HSCT) may lead to durable remission. However, allogeneic HSCT in particular comes with a high risk of treatment-related mortality.

Five agents are currently approved in the United States for the treatment of r/r MCL: the 26S proteasome inhibitor bortezomib, the second-generation thalidomide derivative lenalidomide, and, undergoing confirmatory studies under accelerated approval, the Bruton tyrosine kinase (BTK) inhibitors ibrutinib, acalabrutinib, and zanubrutinib. Key outcomes upon which approval of these drugs was based are summarized in Table 1. Of note, the studies upon which accelerated approval of ibrutinib, acalabrutinib, and zanubrutinib were based evaluated continuous indefinite therapy with the respective BTK inhibitor under investigation until subjects experienced either disease progression or unacceptable toxicity.

Table 1. Primary efficacy results among therapies approved in the United States for treatment of relapsed or refractory mantle cell lymphoma.

Agent	Approval Type	N	ORR	CR	Median DOR (months)
Bortezomib	Traditional	155	48 (31%)	12 (8%)	9.3
Lenalidomide	Traditional	134	34 (26%)	9 (7%)	16.6
Ibrutinib	Accelerated	111	73 (66%)	19 (17%)	17.5
Acalabrutinib	Accelerated	124	100 (81%)	50 (40%)	NE
Zanubrutinib	Accelerated	118	99 (84%)	59 (50%)	18.5, 19.5*

Abbreviations: CR = complete response, DOR = duration of response, NE = not estimable, ORR = objective response rate
**Approval based upon results from two studies, the results of which were reported independently*
(Source: FDA clinical reviewer's compilation from each drug's current prescribing information)

ZUMA-2 studied subjects with r/r MCL after failing BTK inhibitor treatment. Minimal published data exist regarding outcomes in this population. The data which are available illustrate a poor prognostic group, with complete response (CR) rates typically less than 20% and ORRs approaching 53% with a median duration of response (DOR) of 8.1 months at best. The post-BTK inhibitor population demonstrates an unmet medical need and has no approved therapeutic options.

Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) that has been approved by the European Medicines Agency for treatment of r/r MCL. However, in a head-to-head study, temsirolimus therapy demonstrated both poorer progression-free survival and poorer tolerability than ibrutinib in subjects with r/r MCL, and temsirolimus is not approved for any MCL indication in the United States.

Regulatory History
Clinical studies to investigate brexucabtagene autoleucel in B cell malignancies were performed under BB-IND-16675, submitted in October 2015. Orphan designation for MCL was granted in April 2016, and breakthrough designation for MCL was granted in June 2018. BLA format and content were discussed in a Type B meeting in April 2019, and a pre-BLA Type B meeting was held in November 2019. BLA 125703 was submitted 11th December 2019, with a PDUFA action due date of 11th August 2020.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Product description
TECARTUS consists of human autologous CD19-specific chimeric antigen receptor (CAR) expressing T cells generated by in vitro transduction with a gammaretrovirus vector (b) (4), which encodes the CAR transgene but lacks all other elements required for productive replication. The CAR transgene consists of the (b) (4) murine anti-human CD19-specific antibody single chain variable fragment (scFv) fused to human CD28 and the CD3ζ intracellular domain. CAR expression is under control of the (b) (4) This vector is identical to that used in manufacture of axicabtagene ciloleucel (YESCARTA).

Manufacturing Summary
The TECARTUS manufacturing process begins with collection of apheresis material from patients at qualified apheresis centers. The apheresis material is shipped to the Kite Pharma manufacturing facility, where it is processed via washing, followed by enrichment of T cells on the basis of (b) (4) using (b) (4) . Enriched T cells are then activated using anti-CD3 and anti-CD28 mAbs in the presence of IL-2. (b) (4) Activated T cells are then transduced with the (b) (4) vector and expanded in culture until sufficient anti-CD19 CAR T cells are available to meet dose requirements (total culture time is (b) (4) . The culture is then harvested, washed (b) (4) The drug product (DP) is formulated in saline/human serum albumin (HSA)/CryoStor® (b) (4) infusible cryopreservation solution. Each dose is comprised of a fixed number of anti-CD19 CAR T cells calculated based on viable cell count, (b) (4) (determined by (b) (4) for CAR expression) and patient body weight. Formulated DP is filled into cryopreservation bags by (b) (4) methods, with each bag containing one dose in a 68 ml nominal volume. (b) (4) doses of TECARTUS are produced from each manufacturing run. Filled DP bags are cryopreserved and stored at ≤ -150°C in vapor phase liquid nitrogen until lot release testing is complete. Released DP is then shipped frozen to qualified treatment sites for administration back to the same patient.

Manufacturing Controls
Chain of identity/chain of custody (COI/COC) procedures are established once the apheresis material has been collected. These procedures involve tracking the patient-specific material at each step in the manufacturing process from apheresis collection through to infusion of the DP and are critical to maintain control of intermediates and product to ensure that each patient receives the correct, autologous lot of TECARTUS. TECARTUS is manufactured in a (b) (4) from raw materials and reagents that meet acceptable quality standards. Human and animal derived raw materials are appropriately controlled to ensure identity and absence of microbial contaminants. Samples for lot release testing are collected at the appropriate stages in manufacture: (b) (4) endotoxin, and sterility testing samples are drawn from each filled DP bag; DP appearance is assessed in filled bags prior to cryopreservation. Lot release test methods are suitably validated (except for the appearance method, which is a qualified compendial assay) and DP specifications are adequate to ensure product quality and consistency. Note that because the same retroviral vector is used for TECARTUS and YESCARTA, the (b) (4) test cannot distinguish these two products. However, the combination of testing to (b) (4) and robust, validated COI/COC systems for both YESCARTA and TECARTUS is sufficient to maintain control of the product and ensure that each patient's DP is generated by the correct process.

Process Validation
Suitability of the TECARTUS commercial manufacturing process at the Kite Pharma, Inc. (b) (4) manufacturing facility was assessed using healthy donor lots as a part of process performance qualification (PPQ). Testing of PPQ lots included in-process and final product

assessments covering all critical and non-critical process parameters. Performance validation acceptance criteria (PVAC) were prospectively set based on (b) (4) clinical and healthy donor lots using a tolerance interval-based approach at 95% confidence and 95 or 99% tolerance levels. All deviations and exceptional conditions during PPQ studies were investigated and closed. All PPQ lots met lot release specifications, and PPQ studies met the pre-defined PVAC except for (b) (4) levels in the DP, which narrowly exceeded the PVAC in (b) (4) lots. However, there is a wide safety margin (b) (4)-fold for a (b) (4) patient) between the PVAC and the toxicity limit for (b) (4), which is sufficient to mitigate any concerns. Additional PPQ and validation studies included aseptic media fills, assessment of a (b) (4) system, COI/COC, shipping, and (b) (4) vector manufacturing. In addition, an ongoing process verification (OPV) program was established to define, collect, analyze, and respond to trends in process performance and product quality data generated during commercial manufacturing.

Manufacturing Risks, Potential Safety Concerns, and Management

Failure in COI/COC

As it is an autologous product, administration of TECARTUS to the incorrect patient would result in potential risks (including infection, graft versus host disease, and lack of anti-tumor effect). To prevent this, an integrated COI/COC system has been established to track each lot of product from collection of apheresis material, through the manufacturing process, and ultimately to administration of TECARTUS back to the correct patient. This COI/COC system is identical to that previously established for YESCARTA. COI/COC checks are incorporated throughout the TECARTUS manufacturing process and prior to patient administration. The COI/COC system, coupled with training and qualification procedures for apheresis collection centers and treatment sites, was assessed and found to be suitable for its intended purpose.

Replication Competent Retrovirus

A theoretical safety concern in the TECARTUS manufacturing process is generation of replication-competent retrovirus (RCR). (b) (4) are tested by a sensitive method and found negative for RCR in accordance with current FDA guidelines. No RCR has been detected in any clinical studies of TECARTUS or YESCARTA, which is manufactured using the same vector.

Insertional Mutagenesis

Integration of the retroviral vector into the genome of cells comprising TECARTUS could result in insertional mutagenesis. This might unintentionally activate a proto-oncogene or inactivate a tumor suppressor gene, resulting in cellular transformation and eventual secondary malignancies. While the risk of insertional mutagenesis cannot be fully controlled, it is mitigated by ensuring that the average (b) (4) in TECARTUS is limited to (b) (4)

Specifications

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

Table 1. TECARTUS lot release specifications

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

Abbreviations: CAR = chimeric antigen receptor; (b) (4) *quantitative polymerase chain reaction;* (b) (4)

[1] Dose is calculated based on patient weight, viable cell concentration and (b) (4) *(anti-CD19 CAR expression)*

The analytical methods and their validations and/or qualifications reviewed for the brexucabtagene autoleucel DP were found to be adequate for their intended use.

Impurity Profile
TECARTUS consists of $CD3^+$ T cells, which on average comprise (b) (4) of the total cell population in the product. The mean percentage of transduced cells in TECARTUS is (b) (4) with a standard deviation of (b) (4), based on (b) (4) patient lots in the ZUMA-2 study. Impurities can be divided into product-related (cellular impurities derived from the leukapheresis material and dead cells) and process-related impurities (residual manufacturing reagents and ancillary materials that are not intended to be in the final product). Cell viability is controlled during the manufacturing process, and the percentage of viable cells in TECARTUS has been consistently higher than the lot release specification of (b) (4). The frequency of non-$CD3^+$ cells, essentially comprised of natural killer (NK) cells, in TECARTUS was characterized during development and was consistently below (b) (4). Clearance of process-related impurities, including (b) (4), gentamicin, (b) (4). Overall, greater than (b) (4) clearance of process-related impurities was observed based on laboratory testing of the DP. The theoretical clearance of process-related impurities through (b) (4) in the manufacturing process is expected to be greater than (b) (4). A risk assessment was also performed for process-related impurities, which concluded that maximum levels of each potential impurity in the product are within toxicological acceptance limits by a substantial safety margin.

Viral Safety
Potential risks from adventitious viruses and spongiform encephalopathy agents are managed though assessment of source materials and appropriate testing during vector and TECARTUS manufacture. Raw materials of animal, human, or recombinant origin are sourced to minimize risk of potential contamination with spongiform encephalopathy agents. All raw materials are qualified and tested to ensure suitability. Infusion of TECARTUS therefore presents a low risk for infecting patients with adventitious agents.

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

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

CCI testing (CCIT) was performed by Kite on the (b) (4) filled cryobags using (b) (4). The results were acceptable.

Stability
Long-term stability studies on TECARTUS lots stored at ≤ -150°C have been completed out to (b) (4) months for patient lots in the commercial container closure, and healthy donor lots in a scaled-down version of the container closure system. (b) (4)-month long-term stability studies of healthy donor PPQ and post-PPQ lots are ongoing, with data available out to 12 months. Accelerated and stress stability studies (at (b) (4), respectively) have also been completed and reveal that potency (b) (4), and to a lesser extent CAR expression, are

stability-indicating parameters. Based on the totality of available data, the shelf-life of TECARTUS should be set to 12 months at ≤ -150°C. In use stability testing supports a post-thaw expiry of 3 hours. An acceptable post-approval long-term stability protocol, which includes maintenance of sterility testing at the end of the expiry period, is provided.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that brexucabtagene autoleucel is an autologous product; as such each lot will treat a single patient. Failure of a single lot will have 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 brexucabtagene autoleucel 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. Facilities involved in manufacture of brexucabtagene autoleucel and inspectional histories

Name/Address	FEI Number	DUNS number	Inspection / waiver	Justification / Results
Kite Pharma, Inc. (b) (4) • Manufacture, control, and storage of brexucabtagene autoleucel Final Product • All brexucabtagene autoleucel Final Product release testing • (b) (4) Vector release and stability testing • (b) (4) Vector lot disposition	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance Team Biologics VAI
(b) (4) • Manufacture, control, packaging, labeling, and storage of (b) (4) Vector	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance Team Biologics VAI
(b) (4) • Final Release & Stability Testing for DS and DP; raw material testing	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance ORA VAI

ORA (Team Biologics) performed a routine GMP inspection of Kite Pharma, Inc. from (b) (4) . All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

ORA (Team Biologics) performed a routine GMP inspection of (b) (4) All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

ORA performed a routine GMP inspection of (b) (4) . All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

d) Environmental Assessment

A request for categorical exclusion from an Environmental Assessment per 21 CFR 25.31(c) was provided in the BLA. This request and supporting information provided by Kite Pharma is acceptable to conclude that TECARTUS poses a negligible risk to the environment or to the general public. The risk of retroviral vector recombination to a replication competent form is assessed as extremely low to negligible. The potential for the retroviral vector or TECARTUS to persist in the environment is negligible. There is a potential risk for exposure of healthcare staff during product administration, but this can be effectively mitigated by universal precautions that are already established at healthcare facilities and by additional training provided by Kite during treatment site qualification. Overall, there are no significant environmental or public health impacts posed by the retroviral vector or by TECARTUS. Categorical exclusion under 21 CFR 25.31(c) is therefore acceptable.

e) Product Comparability

Studies to demonstrate comparability of products manufactured at the Applicant's clinical manufacturing site (b) (4) and the commercial manufacturing site (b) (4) were performed under IND16675. These studies demonstrated that CD19 CAR-positive T cells manufactured at each site were comparable. No future manufacturing changes to be evaluated under a comparability protocol were proposed in the BLA.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In vitro characterization of KTE-X19 included demonstration of CD19-dependent cytotoxicity, cytokine release, and proliferation when co-cultured with tumor cell lines expressing CD19. Additionally, an in vivo study conducted using an analogous murine CAR construct recognizing the murine CD19 molecule demonstrated anti-tumor activity and increased survival in a lymphodepleted syngeneic adoptive transfer mouse model of $CD19^+$ B cell lymphoma. These studies indicated that the CAR T cells could target normal B cells, however, no other effects on the overall health of the animals were observed.

Traditional in vitro and in vivo genotoxicity and carcinogenicity/tumorigenicity assessments of KTE-X19 were not conducted. Published clinical and nonclinical data derived from different CAR T products supports a relatively low risk for malignant transformation of T cells by retroviral vectors. Additionally, vector integration analysis conducted using a similar

product, which uses the same retroviral vector and anti-CD19 CAR transgene as KTE-X19, found the integration profile consistent with published data for similar vectors.

No animal reproductive and developmental toxicity studies were conducted with KTE-X19, which is acceptable based on the product characteristics and safety profile.

5. CLINICAL PHARMACOLOGY

The clinical pharmacology section of this BLA is supported by one Phase 2 clinical study (ZUMA-2) that evaluated the efficacy, safety, pharmacokinetic (PK) and pharmacodynamics (PD) of TECARTUS in adult subjects with relapsed or refractory mantle cell lymphoma (r/r MCL). Subjects were enrolled into 2 separate dose cohorts and treated to evaluate the efficacy of TECARTUS.

- Cohort 1: Cohort 1 is the pivotal Cohort with a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum dose of 2×10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg). The primary endpoint analysis was conducted with the first 60 subjects in Cohort 1 who were treated with TECARTUS. At the time of the data cutoff date of July 24, 2019, 68 subjects received TECARTUS in Cohort 1.
- Cohort 2: Cohort 2 has a target dose of 0.5×10^6 anti-CD19 CAR T cells/kg (maximum dose of 0.5×10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg). At the time of the data cutoff date of July 24, 2019, 14 subjects received TECARTUS in Cohort 2.

Subjects received a single intravenous (IV) infusion of TECARTUS on Day 0 after receiving 3 days of conditioning chemotherapy (fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day) on Day -5 through Day -3.

The key clinical pharmacology findings of TECARTUS in adult subjects with r/r MCL are as follows:

- General pharmacokinetics/cellular kinetics of TECARTUS:
  - Following infusion, TECARTUS exhibited an initial rapid expansion phase followed by a rapid decline and then a gradual decrease. The median time to reach peak levels of TECARTUS in blood was 15 days post-infusion.
  - At the dose of 2×10^6 anti-CD19 CAR T cells/kg, TECARTUS levels decreased to near baseline at Month 3 post-infusion. TECARTUS was detectable in some adult subjects with r/r MCL for up to 24 months in peripheral blood at the time of the data cutoff date.
  - At the dose of 0.5×10^6 anti-CD19 CAR T cells/kg, the peak levels and $AUC_{0\text{-}28d}$ of TECARTUS were approximately 60% of that in subjects treated at the dose of 2×10^6 anti-CD19 CAR T cells/kg. TECARTUS decreased to undetectable levels in the majority of evaluable subjects by 15 months post-infusion.

- TECARTUS pharmacokinetics/cellular kinetics in specific populations:
  - TECARTUS exposure (Cmax and $AUC_{0\text{-}28d}$) was numerically higher in subjects < 65 years of age compared to subjects ≥ 65 years of age. However,

with limitations imposed by high inter-subject variability of TECARTUS exposure, small sample size, and other factors such as tumor burden, the impact of age on TECARTUS exposure should be interpreted with caution.
    - TECARTUS exposure was similar between male and female subjects.
    - Baseline tumor burden did not show a monotonic association with TECARTUS expansion.
    - Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with TECARTUS. Subjects who received both tocilizumab and corticosteroids had higher TECARTUS exposure than subjects who received either medication alone or neither medication. These observations are confounded by the fact that the need for tocilizumab and/or corticosteroids was triggered by toxicity, which was associated with higher TECARTUS exposures.
- After infusion, substantially higher median values of Cmax and $AUC_{0\text{-}28d}$ of TECARTUS were reported in responders [complete response (CR) and partial response (PR)] compared to non-responders.
- Higher TECARTUS exposures (Cmax and $AUC_{0\text{-}28d}$) were reported in subjects with higher grades of CRS or neurologic event (Grade 3 or higher versus Grade 2, Grade 1, or no events).
- After TECARTUS infusion, substantial elevations in peak serum levels and $AUC_{0\text{-}28d}$ were observed in subjects with Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1, or no CRS for the following biomarkers: ferritin, granzyme B, IL-2Rα, IL-6, IL-8, IL-10, IL-15, perforin, and TNF-α.
- After TECARTUS infusion, substantial elevation in peak serum levels and $AUC_{0\text{-}28d}$ were observed in subjects with Grade 3 or higher neurologic event compared to subjects with Grade 2, Grade 1, or no neurologic event for the following biomarkers: granzyme B, IFN-γ, IL-1RA, IL-2, IL-6, IL-10, IL-15, and TNF-α.
- Cytokines and immune effector molecules were evaluated in available cerebrospinal fluid (CSF) samples (n=17):
    - Levels of three pro-inflammatory cytokines (CRP, CXCL-10, and IL-6) were at least 5-fold higher than the median baseline values.
    - Median levels of the following analytes were substantially elevated in the CSF of subjects with Grade 3 or higher neurologic events compared to levels in subjects who had Grade 2, Grade 1, or no neurologic events: CRP, ferritin, ICAM-1, IL-2Rα, IL-6, IL-8, and VCAM-1.

  Due to high inter-subject variability and small sample size, the data should be interpreted with caution.
- TECARTUS induced B cell aplasia in the majority of the treated subjects. Median B cell levels recovered to 10.62% (range: 3.97-15.99%) by Month 18 in evaluable subjects.
- There was no reported presence of replication-competent retrovirus (RCR) in the blood of TECARTUS-treated subjects.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The clinical review team's recommendation for accelerated approval of TECARTUS for the treatment of adults with relapsed or refractory (r/r) mantle cell lymphoma (MCL) is based on the clinical study ZUMA-2.

Study Description

ZUMA-2 is a single-arm, Phase 2, multicenter study of the efficacy and safety of TECARTUS in subjects with r/r MCL who had previously been treated with anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a Bruton tyrosine kinase (BTK) inhibitor. The primary endpoint was objective response rate (ORR), defined as rate of complete responses (CRs) plus rate of partial responses (PRs), as determined by an Independent Radiology Review Committee (IRRC) applying the 2014 Lugano Classification criteria. Key secondary endpoints were duration of response (DOR) and subject incidence of each class of best objective response (BOR). Primary efficacy analyses were performed in the prospectively identified Inferential Analysis Set (IAS), comprised of the first 60 subjects to be infused with 2×10^6 CAR-positive viable T cells per kilogram body weight and have the opportunity to be followed for at least six months after their first objective disease response. Bridging therapy with corticosteroids and/or BTK inhibitors was allowed at the investigators' discretion during product manufacturing.

Clinical Efficacy

Demographics and Disposition

Leukapheresis was performed on 74 subjects. Of these, 69 (93%) began conditioning chemotherapy, 68 (92%) were treated with TECARTUS, and, per IAS definition, 60 (81%) with follow-up of at least six months after first objective disease response were included in primary efficacy analyses. Among the 60 efficacy-evaluable subjects, the median time from leukapheresis to TECARTUS delivery was 15 days (range 11-28 days). This population was, as expected, predominantly male (51 of 60; 85%) and Caucasian (56 of 60; 93%). The group had a median age of 65 years (range 38 to 79) and had received a median of three (range two to five) prior lines of therapy. One-third of the subjects (18 of 60; 30%) had tumors with blastoid or pleomorphic histology, 43% (26 of 60) had failed autologous hematopoietic stem cell transplantation, nearly two-thirds (36 of 60; 60%) were refractory to their most recent prior line of MCL therapy, and all (100%) had been exposed to at least one BTK inhibitor.

Primary Endpoint

Results of the primary endpoint analysis are shown in Table 3 and demonstrate an ORR of 87%.

Table 3. ZUMA-2 objective response rate (ORR); central analysis per 2014 Lugano Classification (IAS, n = 60).

	FDA Analysis % (n), [95% CI]
ORR	87% (52), [75.4 – 94.1]

Abbreviation: CI = confidence interval

(Source: FDA clinical reviewer; based on BLA 125703/0.0, 5.3.5.2 Data Tabulation Data datasets; Data Analysis Data datasets; case report forms; Report Body Table 13, page 74 of 997; and multiple information requests)

Four subjects (7%) in the IAS (n = 60) were reclassified by FDA from responders (one CR, three PRs) to non-responders [one progressive disease (PD), three non-evaluable (NE)]. Baseline disease burden was unclear in three of the four subjects, and as such their post-treatment disease responses could not be accurately evaluated. The fourth subject was assessed by central evaluators as having a PR at the first post-treatment follow-up timepoint based on imaging review; however, they did not have access to the investigator's physical exam findings, which revealed PD in the form of worsening skin lesions.

Secondary Endpoints

Best Objective Response

Subjects' best objective responses (BORs) are displayed in Table 4. The majority of subjects treated with TECARTUS responded with CRs, while an additional quarter experienced PRs. During the efficacy analysis, two subjects (3%) were reclassified by FDA from BOR of CR to BOR of PR, which did not alter the overall efficacy conclusions. For details, please see the clinical review memorandum.

Table 4. Best objective responses in ZUMA-2; central analysis per 2014 Lugano Classification (IAS, n = 60).

	FDA Results n (%) [95% CI]
CR	37 (62%) [48.2 – 73.9]
PR	15 (25%) [14.7 – 37.9]
SD	2 (3%) [0.4 – 11.5]
PD	3 (5%) [1.0 – 14.0]
NR	3 (5%) [1.0 – 14.0]

Abbreviations: CI = confidence interval, CR = complete response, IAS = inferential analysis set, n/a = not applicable, NR = non-responder, PD = progressive disease, PR = partial response, SD = stable disease

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Data Tabulation Data datasets; Data Analysis Data datasets; case report forms; Report Body Table 13, page 74 of 997; and multiple information requests)

Duration of Response

Table 5 compiles DOR observations. A 69% rate of censoring after a median of 240 days of follow-up from the time of first response precluded estimation of a median DOR. FDA adjudicated the Applicant's reported DOR for three (5%) subjects, primarily by application of ZUMA-2's imaging charter's date selection criteria and timepoint response assessment guidance. These adjustments did not substantially alter the DOR results.

Table 5. Duration of response results in ZUMA-2; FDA analysis (IAS, n = 60).

	Inferential Analysis Set (N = 60)
Number of Responders	52
Duration of response (days) Estimated median (95% CI)	NE (358, NE)
Median follow-up time (min, max)	240 (0, 888)
Percentage censored	69%
DOR if BOR is CR (days)	
Estimated median (95% CI)	NE (413, NE)
Median follow-up time (min, max)	252 (56, 888)
Percentage censored	84%
DOR if BOR is PR (days)	
Estimated median (95% CI)	129 (48, 358)
Median follow-up time (min, max)	65 (0, 672)
Percentage censored	33%

Abbreviations: BOR = best objective response, CI = confidence interval, CR = complete response, DOR = duration of response, max = maximum, min = minimum, NE = not estimable, PR = partial response

(Source: FDA statistical reviewer)

Efficacy Review Issues

The primary efficacy review issue was lack of sufficient follow-up to adequately assess DOR. Although treatment with TECARTUS resulted in a favorable ORR during ZUMA-2, the data were unable to show sufficient DOR to demonstrate clinical benefit and support traditional approval. The proposed indication of r/r MCL was a second review issue. All r/r MCL patients comprise a significantly broader population than that studied in ZUMA-2, most notably differing in a requirement for prior BTK inhibitor therapy in the latter. No data exist on the efficacy of TECARTUS in BTK inhibitor-naïve patients with r/r MCL to confirm clinical benefit in this group. These review issues can be addressed through postmarketing requirements (PMRs) as discussed below in section 7 c) Recommendation for Postmarketing Activities.

A third issue arose during review of TECARTUS' proposed prescribing information, where dosing was described in terms of a "target dose". Fifty-four (90%) of the efficacy-evaluable subjects were infused with 2×10^6 CAR-positive viable T cells/kg, while the six (10%) remaining subjects were administered smaller doses. The subset treated with a dose other than 2×10^6 CAR-positive viable T cells/kg is too small to support efficacy conclusions. As such, the prescribing information language was changed from "target dose" to "dose", and TECARTUS' lot release dose criterion was revised from a range to the single data-supported value.

Bioresearch Monitoring
Bioresearch Monitoring (BIMO) inspections were conducted at three domestic clinical study sites that participated in the conduct of study KTE-X19-102 (ZUMA-2). The inspections did not reveal any issues that impact the data submitted in this original Biologics License Application (BLA).

Efficacy Conclusions
ZUMA-2 studied patients with MCL which had relapsed after or was refractory to anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a BTK inhibitor. However, the clinical review team believes extrapolation of ZUMA-2's efficacy conclusions to the broader r/r MCL population, without restriction based on BTK inhibitor exposure, is appropriate based on the following:

1. BTK inhibitors are currently approved under accelerated approval to address the unmet medical need of patients with r/r MCL, and there are no FDA-approved treatments of any approval type for patients with r/r MCL after failing BTK inhibitors. ZUMA-2 therefore evaluated TECARTUS in a population with no FDA-approved therapies available, even under accelerated approval, who had received a median of three prior lines of therapy. Notable pre-study exposures included autologous hematopoietic stem cell transplant in 43% of subjects, anthracyclines in 72%, and bendamustine in 54%. This describes a poor-prognosis population with advanced disease.
2. The observed ZUMA-2 ORR of 87%, CR rate of 62%, and not estimable median duration of response after median follow-up of 240 days from time of first response represent robust results in the population under study.
3. To evaluate the response to TECARTUS in subjects with limited or no exposure to BTK inhibitors and inform a decision regarding expansion of the indicated treatment population to r/r MCL regardless of BTK inhibitor exposure, the clinical team examined ZUMA-2 for subjects with limited or no exposure to BTK inhibitors. Consistent with the study's eligibility criteria, only one subject met these parameters. As a result, no meaningful conclusions could be drawn. However, there is no apparent mechanistic reason to suggest that patients with r/r MCL who have not been exposed to BTK inhibitors would experience decreased rate, depth, or durability of response after treatment with TECARTUS than those who have been exposed to BTK inhibitors. The clinical team therefore considers ZUMA-2's efficacy data sufficient to extrapolate to the broader r/r MCL population that has not necessarily been treated with BTK inhibitors.
4. Because the clinical team's recommendation to grant accelerated approval for the broad r/r MCL indication includes assumptions regarding TECARTUS' efficacy in BTK inhibitor-naïve patients, the clinical team further recommends confirmation of TECARTUS' efficacy in BTK inhibitor-naïve subjects to justify consideration of conversion to traditional approval. To accomplish this, the clinical team recommends a postmarketing requirement (PMR) for a study of TECARTUS treatment of BTK inhibitor-naïve subjects with a minimum follow-up of 18 months from the time of first response. This will facilitate evaluation of both response rate and durability of response in the context of agents currently under accelerated approval for this population. Additionally, because the BTK inhibitor-naïve PMR study will utilize a single-arm design to allow adequate subject accrual within a reasonable timeframe, the clinical team recommends a second PMR study to provide supporting evidence of response durability. This second PMR study should comprise additional follow-up

of the subjects already treated in ZUMA-2 to a minimum of 18 months from time of first objective response. Within the recommended framework of accelerated approval for the broad indication of r/r MCL with two efficacy PMRs, the ORR and durability of response observed in ZUMA-2 thus far serve as an intermediate clinical benefit endpoint supporting accelerated approval for r/r MCL. The ORR, CR rate, and durability of response after a minimum follow-up of 18 months from time of first response observed in BTK inhibitor-naïve subjects define a clinical benefit endpoint that may support traditional approval, while additional follow-up for durability of response in subjects already treated on ZUMA-2 will provide supportive data for the durability of response seen in BTK inhibitor-naïve subjects.

5. Finally, the clinical review team considered recommending traditional approval for the population of BTK inhibitor-exposed patients with r/r MCL after treatment with an anti-CD20 monoclonal antibody and chemotherapy containing an anthracycline or bendamustine represented by the subjects in ZUMA-2. However, this narrower population is included within the broader r/r MCL population for which the limitations of the durability data preclude traditional approval, and as such the clinical review team considered a separate approval unnecessary.

In summary, ZUMA-2 represents an adequate and well controlled trial that demonstrated high response rates, and preliminary DOR observed after treatment with TECARTUS in the poor prognosis, BTK inhibitor-exposed r/r MCL population studied in ZUMA-2 suggests a reasonable expectation that treatment of the broader r/r MCL population with TECARTUS may lead to clinically meaningful efficacy. The basis for FDA's conclusion of substantial evidence of effectiveness is the substantial magnitude of benefit primarily driven by durable complete response rate in a disease condition where durable complete response rates are dismal. Therefore, the results of ZUMA-2, although a single adequate and well controlled study, support accelerated approval from an efficacy perspective, with confirmation of clinically meaningful benefit in the BTK inhibitor-naïve r/r MCL population, supported by additional follow-up of the already-treated ZUMA-2 subjects, needed to inform a decision regarding traditional approval for the broad indication of r/r MCL.

b) Pediatrics

TECARTUS received orphan drug designation (ODD) on 28 April 2016 for the treatment of mantle cell lymphoma. Per the Pediatric Research Equity Act (PREA) and 21 Code of Federal Regulations (CFR) 314.55(d), ODD products are exempt from pediatric study requirements. As such, the Applicant did not include a pediatric assessment in this BLA.

c) Other Special Populations

TECARTUS has not been studied in any special populations.

6. SAFETY

The primary safety population for ZUMA-2 included a total of 82 subjects who were treated with TECARTUS (68 subjects from Cohort 1 and 14 subjects from Cohort 2). All 82 subjects (100%) had at least one adverse event (AE) that occurred after the administration of TECARTUS. Ninety-eight percent (n=80) experienced Grade 3 or higher events. Serious

adverse events (SAEs) were observed in 54 (65%) of the subjects, and SAE Grade 3 or higher occurred in 44 (53%) subjects. Adverse events of special interest (AESI) included cytokine release syndrome (CRS), neurologic toxicities, serious infections, febrile neutropenia, prolonged cytopenias lasting greater than 30 days, and hypogammaglobulinemia. CRS was reported and graded per Lee 2014 criteria.

The table below summarizes the adverse events of special interest

Table 6. Adverse Events of Special Interest

Study ZUMA-2	**Any Grade N = 82 n (%)**	**Grades ≥3 n (%)**
CRS	75 (91%)	15 (18%)
Neurologic Toxicities	66 (80%)	30 (37%)
Infections	47 (57%)	26 (32%)
Prolonged Cytopenia*	62 (76%)	46 (56%)
Hypogammaglobulinemia	13 (16%)	1 (1%)

**Febrile neutropenia occurred in five subjects (6%)*
(Source: FDA clinical review)

The following table summarizes AEs that were observed in at least 10% of subjects following TECARTUS infusion.

Table 7. Most Frequent Adverse Events Following TECARTUS Infusion

Body System Organ Class	**Preferred Terms ***	**All Grades N (%)**	**Grades 3 or Higher N (%)**
Blood and lymphatic system	Neutropenia *	71 (87%)	70 (85%)
	Anemia	53 (65%)	40 (49%)
	Thrombocytopenia	57 (70%)	31 (50%)
	Leukopenia	48 (59%)	47 (57%)
	Lymphopenia	17 (21%)	14 (17%)
Cardiac disorders	Tachycardia	38 (46%)	0 (0%)
	Arrhythmia	18 (22%)	3 (4%)
Eye disorders	Vision Blurred	13 (16%)	0 (0%)
Gastrointestinal disorders	Diarrhea	24 (29%)	5 (6%)
	Nausea	30 (37%)	1 (0%)
	Vomiting	10 (12%)	0 (0%)
	Constipation	24 (29%)	0 (0%)
	Abdominal Pain	14 (17%)	0 (1%)
	Dysphagia	9 (11%)	2 (2%)
General disorders and Administration site	Fever	77 (94%)	12 (15%)
	Fatigue	39 (48%)	2 (2%)
	Chills	34 (41%)	0 (0%)

Body System Organ Class	Preferred Terms *	All Grades N (%)	Grades 3 or Higher N (%)
	Edema	29 (35%)	2 (2%)
	Pain	11 (13%)	2 (2%)
Immune system disorders	Hypogammaglobulinemia	13 (16%)	1 (1%)
	Cytokine Release Syndrome #	75 (91%)	15 (18%)
Infections and infestations	Infections Pathogen unspecified	35 (43%)	23 (28%)
	Viral infection	14 (17%)	4 (5%)
	Bacterial infection	13 (16%)	6 (7%)
	Pneumoniae **	15 (17%)	10 (12%)
	Fungal infection	8 (10%)	0 (0%)
Metabolism and nutrition	Hypophosphatasemia	30 (37%)	18 (22%)
	Hypoalbuminemia **	27 (33%)	2 (2%)
	Hypokalemia	26 (32%)	5 (6%)
	Hyponatremia	26 (32%)	10 (12%)
	Hypocalcemia	23 (28%)	5 (6%)
	Decreased appetite	21 (26%)	0 (0%)
	Hyperglycemia	18 (22%)	6 (7%)
	Hypomagnesaemia	14 (17%)	0 (0%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain **	29 (35%)	1 (1%)
	Motor Dysfunction	14 (17%)	3 (4%)
Nervous system disorders	Encephalopathy **	43 (52%)	19 (23%)
	Tremor **	32 (39%)	2 (2%)
	Headache	29 (35%)	1 (1%)
	Aphasia **	19 (23%)	7 (6%)
	Neuropathy **	16 (20%)	2 (2%)
	Dizziness **	15 (18%)	6 (7%)
Psychiatric disorders	Delirium **	13 (16%)	4 (5%)
	Insomnia	17 (21%)	0 (0%)
	Anxiety	14 (17%)	0 (0%)
Renal and urinary disorders	Renal Insufficiency	10 (12%)	6 (7%)
	Urinary Retention	8 (10%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	33 (40%)	16 (20%)
	Cough	31 (38%)	0 (0%)
	Dyspnea	20 (24%)	5 (6%)
	Pleural Effusion	17 (21%)	4 (5%)
	Pulmonary Edema	10 (9%)	3 (3%)
Skin and subcutaneous tissue	Rash	16 (20%)	2 (2%)
Vascular disorders	Hypotension	47 (57%)	22 (27%)
	Hypertension	15 (18%)	9 (11%)
	Thrombosis	12 (15%)	1 (1%)

** includes laboratory investigations reported as AEs*

*** includes FDA grouped terms*

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

(Source: FDA clinical review)

Altogether, 20 deaths were reported from the time of informed consent to the data cut-off for the study (July 24, 2019). Fifteen subjects died of progressive disease, and one death was attributed to the product as per FDA analysis. Three deaths occurred within 30 days of TECARTUS infusion.

The median time to onset of CRS was three days (range 1 to 13 days), and the median time to resolution was 10 days (range 1 to 50 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, hypotension, and hypoxia. Sixty-two percent (51 of 82) of subjects received tocilizumab for CRS management.

The median time to onset of neurological toxicity was six days (range 1 to 32 days). The median duration was 21 days in subjects for whom neurotoxicity resolved. Prolonged encephalopathy lasting up to 187 days was noted. The most common neurological toxicities included encephalopathy, tremor, headache, aphasia, anxiety, dizziness, and delirium. Neurological toxicities were managed with supportive care and/or corticosteroids. Almost all Grade ≥ 2 neurologic toxicities occurred within seven days following TECARTUS infusion.

Acquired hypogammaglobulinemia due to the loss of normal B cells after treatment with TECARTUS was observed, and subjects were maintained on supplemental treatment with intravenous gamma globulin.

TECARTUS 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. None of these outcomes have been observed in ZUMA-2 to date, but subjects remain on 15 year long-term follow up to detect such delayed adverse events.

Grade 3 or 4 laboratory abnormalities occurring in ≥ 10% of subjects included: leukopenia (95%), neutropenia (95%), lymphopenia (86%), thrombocytopenia (65%), anemia (54%), hypophosphatemia (31%), hypocalcemia (21%), increased alanine aminotransferase (15%), and hypokalemia (10%).

<u>Risk Evaluation and Mitigation Strategies (REMS):</u>
During the conduct of the ZUMA-2 study, life-threatening adverse events attributed to TECARTUS 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 life-threatening adverse reactions warrant warnings, including a boxed warning for CRS and neurological toxicity. FDA determined that a REMS is indicated to ensure that the benefits of TECARTUS outweigh the risks of CRS and neurological toxicities.

YESCARTA (axicabtagene ciloleucel), a CD19-directed, genetically modified autologous T cell immunotherapy, was licensed on October 18, 2017 to treat 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. Due to the serious risks of CRS and neurological toxicities associated with YESCARTA (axicabtagene ciloleucel), it was approved with a REMS. The YESCARTA REMS includes goals and elements to assure safe use (ETASU) identical to those necessary for the safe use of TECARTUS. Due to the similar serious risks of CRS and neurological toxicities, and in order to minimize burden on the healthcare delivery system [section 505-1(f)(2)(D)], the REMS for YESCARTA and TECARTUS have been merged into a single "YESCARTA and TECARTUS REMS Program" and consequently, subject to the same REMS assessment plan, and subsequent REMS assessments.

This REMS includes ETASU to mitigate the known risks of CRS and neurological toxicities by:

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

The REMS ETASU requires Kite to ensure that:

- Hospitals and their associated clinics are enrolled in The YESCARTA and TECARTUS REMS Program
- Relevant staff prescribing, administering, or dispensing YESCARTA and/or TECARTUS are enrolled through a training program and knowledge assessment.
- Certified sites report serious cases of CRS and neurological toxicities.
- Kite maintains documentation that processes and procedures are followed for the YESCARTA and TECARTUS 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 or TECARTUS infusion.

Materials provided as part of the REMS include:

- YESCARTA and TECARTUS REMS Program Training
- YESCARTA and TECARTUS REMS Program Knowledge Assessment
- YESCARTA and TECARTUS REMS Program Hospital Enrollment Form
- YESCARTA and TECARTUS REMS Program Website
- YESCARTA and TECARTUS REMS Program Patient Wallet Card
- YESCARTA and TECARTUS REMS Program Adverse Reaction Management Guide

Long-term safety after treatment with TECARTUS, particularly from the risk of insertional mutagenesis-related secondary malignancies, remains 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 the marketed product, including key early adverse reactions and follow-up for 15 years for detection and evaluation of secondary malignancies. Collection and analysis of blood and biopsy specimens of certain malignancies for evaluation of RCR or insertional mutagenesis is part of the 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 500 subjects enrolled within three months of the TECARTUS infusion over a period of five years. All enrolled subjects will be followed for 15 years from their TECARTUS infusion. Patients will receive clinical evaluation and follow-up according to standard of care for patients with relapsed/refractory mantle cell lymphoma. The primary endpoint will be evaluation for secondary malignancy, which will include blood and/or 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 is:

Final Protocol Submission: August 31, 2020
Study Completion: August 31, 2040
Final Report Submission: August 31, 2041

7. ADVISORY COMMITTEE MEETING

TECARTUS is similar to other approved CD19-directed genetically modified autologous T cell immunotherapies, including YESCARTA, and did not raise new or unique scientific or regulatory issues; as a result, an advisory committee meeting was deemed not necessary.

8. OTHER RELEVANT REGULATORY ISSUES

None.

9. LABELING

The proposed proprietary name, TECARTUS, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 16, 2020, and was deemed acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on January 28, 2020.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information (PI), package and container labeling on May 18, 2020, and found them acceptable from a promotional and comprehension perspective.

10. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review team recommends accelerated approval of TECARTUS for the treatment of patients with relapsed or refractory mantle cell lymphoma.

b) Risk/ Benefit Assessment

This BLA is under consideration for accelerated approval, based on an effect on an intermediate clinical endpoint that is reasonably likely to predict clinical benefit (21 CFR 601.41). In the clinical review team's assessment, TECARTUS has demonstrated a favorable objective response rate (ORR) and complete response (CR) rate at six months (median follow-up of 240 days). The six-month ORR and CR rates are intermediate clinical endpoints that are reasonably likely to predict a clinical benefit, represented by ORR and CR rate at 18 months.

Traditional approval in the future would be based on demonstrating durability of response with follow-up of subjects for a minimum of 18 months in relapsed or refractory MCL and supported by data that includes an extended observation period of 18 or more months for each of the 68 subjects in this BLA submission, who received treatment under the ZUMA-2 study, who were refractory to or relapsed following BTK inhibitor therapy.

For the purpose of approval in relapsed or refractory mantle cell lymphoma, the magnitude of ORR and CR rate observed in the ZUMA-2 population is substantial. The safety results demonstrate an acceptable safety profile when implemented with Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU) REMS for the management of Cytokine Release Syndrome (CRS) and neurological toxicities, which represent life-threatening adverse reactions. However, given the life-threatening nature of the disease in the indicated population, these adverse reactions, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective, particularly so with the magnitude of benefit observed with respect to CR rates. Thus, the overall benefit-risk profile favors approval of TECARTUS in patients with relapsed or refractory mantle cell lymphoma.

c) Recommendation for Postmarketing Activities

The clinical review team recommends:

1. Registry study: 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 500 subjects who will be followed for 15 years after their TECARTUS infusion. This study is observational and focuses on short-term toxicity, documenting adverse events, and long-term follow-up for evaluation of secondary malignancies; which will include blood and/or tissue work up for these events. The Applicant plans to enroll approximately 500 patients and follow each for 15 years.

   The timetable for the PMR study is:

   Final Protocol Submission: August 31, 2020
   Study Completion: August 31, 2040
   Final Report Submission: August 31, 2041

2. Additional follow-up of all 68 subjects treated in ZUMA-2 Cohort 1 to a minimum of 18 months from the time of first response: Data will continue to be collected from ZUMA-2 Cohort 1 subjects according to the protocol's established schedule of

assessments until all 60 IAS subjects have had the opportunity for at least 24 months' follow-up from their time of first response and the remaining eight treated subjects have had the opportunity for at least 18 months' follow-up from their time of first response.

- Final protocol submission: Completed. Most recent protocol amendment submitted 13 November 2018
- Study completion: 31 December 2020
- Final study report submission: 31 July 2021

3. Study of TECARTUS treatment of subjects with r/r MCL who have not been exposed to a BTK inhibitor: The Applicant will conduct a single-arm study of 86 BTK inhibitor-naïve subjects with r/r MCL, which accounts for a 10% drop-out rate while providing 90% power to detect a difference between an ORR of 75% after treatment with TECARTUS and an historical ORR of 57%. The study will be conducted by adding a new cohort of BTK inhibitor-naïve subjects to ZUMA-2, with a minimum follow-up of 18 months after first objective disease response. The single-arm structure will facilitate adequate subject accrual within a reasonable timeframe. Details of the full protocol will be finalized prior to implementation.
    - Final protocol submission: 15 January 2021
    - Study completion: 30 April 2025
    - Final study report submission: 31 October 2025