BLA Clinical Review Memorandum

Application Type	Original application
STN	125703
CBER Received Date	11 December 2019
PDUFA Goal Date	10 August 2020
Division / Office	Division of Clinical Evaluation and Pharmacology/Toxicology / Office of Tissues and Advanced Therapies Division of Hematology Malignancies 2 / Office of Oncologic Diseases
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Megan Zimmerman (Efficacy) Helkha Peredo Pinto (Safety)
Review Completion Date / Stamped Date	23 July 2020
Supervisory Concurrence	Margret Merino, MD Bindu George, MD Marc Theoret, MD
Applicant	Kite Pharma, Inc
Established Name	Brexucabtagene autoleucel (KTE-X19)
(Proposed) Trade Name	TECARTUS
Pharmacologic Class	CD19-directed, genetically modified, autologous T cell immunotherapy
Formulation(s), including Adjuvants, etc.	Cryopreserved in a medium containing human albumin (b) (4), sodium chloride (b) (4) and CryoStor (b) (4) (contains (b) (4) dimethylsulfoxide). Supplied in one or more patient-specific infusion bags. Each bag of a nominal 68 ml of KTE-X19 contains (b) (4) chimeric antigen receptor (CAR) T cells/kg.
Dosage Form(s) and Route(s) of Administration	For autologous use only. For intravenous (IV) use only.
Dosing Regimen	Single target dose of 2 x 10^6 CAR-positive viable T cells/kg body weight (maximum 2 x 10^8 CAR-positive viable T cells) administered by 30-minute IV infusion. Preceded by fludarabine and cyclophosphamide lymphodepleting conditioning chemotherapy.
Indication(s) and Intended Population(s)	Proposed: For the treatment of adult patients with relapsed or refractory mantle cell lymphoma
Orphan Designated (Yes/No)	Yes (granted 28 April 2016)

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
Allo	allogeneic
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
Auto	autologous
BLA	biologics license application
BOR	best objective response
CAR	chimeric antigen receptor
CBER	Center for Biologics Evaluation and Research
CMC	chemistry, manufacturing, and controls
CI	confidence interval
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
DLT	dose-limiting toxicity
DOR	duration of response
eCTD	electronic common technical document
ECOG	Eastern Cooperative Oncology Group
EEG	electroencephalogram
EQ-5D	European Quality of Life-5 Dimensions
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
IAS	inferential analysis set
IND	investigational new drug application
IP	investigational product
IPI	International Prognostic Index
ISS	integrated summary of safety
IQR	interquartile range
IRC	independent review committee
IR	information request
IV	intravenous; intravenously
IWG	International Working Group
LTFU	long-term follow-up
MAS	macrophage activation syndrome

MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
mITTAS	modified intent to treat analysis set
mL	milliliter
MMSE	mini mental status exam
MRI	magnetic resonance imaging
NaCl	sodium chloride
NE	not evaluable; not estimable; neurotoxicity events
NESI	neurotoxicity events of special interest
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	prescribing information; package insert
PK/PD	pharmacokinetics/pharmacodynamics
PO	*per os*; orally; by mouth
PREA	Pediatric Research Equity Act
PR	partial response
PS	performance status
PT	preferred term
RCR	replication competent retrovirus
REMS	risk evaluation and mitigation strategy
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SOC	system organ class
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SPD	sum of the products of the perpendicular diameters
TEAE	treatment-emergent adverse event
TTR	time to response
uL	microliter
ULN	upper limit of normal
VAS	visual analog scale

1. EXECUTIVE SUMMARY

Brexucabtagene autoleucel (KTE-X19) is an autologous chimeric antigen receptor (CAR) T cell product engineered to recognize the transmembrane glycoprotein CD19. Critical CAR components are the anti-CD19 single-chain variable fragment and the T cell activating domains of CD3-zeta and CD28, which are all linked. When KTE-X19 engages CD19-positive targets, the modified T cells receive signals to activate and proliferate in order to eliminate the targets. CD19 expression is restricted to the B cell lineage. It is expressed by healthy B cells and retained by most malignancies that arise from B cells, including mantle cell lymphoma (MCL).

The applicant's proposed indication for this product is the treatment of relapsed or refractory (r/r) MCL. In support of this proposal, the applicant submitted safety and efficacy data from the clinical study ZUMA-2, as well as supplemental safety data from ZUMA-3, ZUMA-4, and ZUMA-8.

ZUMA-2 is a single arm, Phase 2, multicenter study of the efficacy and safety of KTE-X19 in subjects with r/r MCL who have previously been treated with anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a Bruton tyrosine kinase (BTK) inhibitor. The primary endpoint is objective response rate (ORR) as determined by an Independent Radiology Review Committee (IRRC) applying the 2014 Lugano Classification criteria. Key secondary endpoints are duration of response (DOR) and subject incidence of each class of best objective response (BOR).

There is limited information in patients who have r/r MCL after treatment with BTK inhibitors. In one retrospective study of patients whose disease was r/r to BTK inhibitors (5.5 Literature Reviewed reference 3), 63% of patients had received two or fewer lines of treatment prior to BTK inhibitors. These included anthracycline-based regimens (19%); hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper CVAD, 83%); bendamustine (31%); and bortezomib (43%). These patients were treated with post-BTK inhibitor salvage regimens. The ORR rate was 32%, complete response (CR) rate was 19%, and median overall survival (OS) was 8.1 months. Another study (5.5 Literature Reviewed reference 9) evaluated the effect of venetoclax monotherapy in patients whose disease was r/r to BTK inhibitors and whom had received a median of three prior lines of therapy. The ORR was 53% [18% CRs; 35% partial responses (PRs)]. The median time to response on venetoclax was 48 days (range 14 to 204 days). The median duration of response was 8.1 months [95% confidence interval (CI) 2.8 – 9.8]. In a third study (5.5 Literature Reviewed reference 17), 35 patients whose disease was r/r to BTK inhibitors but whom did not have prior exposure to bendamustine were treated with rituximab, bendamustine, and cytarabine (R-BAC). The ORR was 82% and the CR/unconfirmed CR (CRu) rate was 56%. Nine subjects received allogeneic hematopoietic stem cell transplant (HSCT) as consolidation. Of the 13 subjects evaluable for response, five remained in remission for 12 months. Although the ORRs are substantial in this patient population with MCL which was r/r following BTK inhibitors, the population is different from the ZUMA-2 population. In ZUMA-2, 72% had received anthracycline-based therapy, 54% had received bendamustine, and 43% had received prior autologous HSCT. Thus, patients whose MCL is r/r to BTK inhibitors after a median of three prior lines of therapy represent a poor prognostic group. CR rates typically are less than 20%, and ORRs at best approach 53%.

Primary efficacy analyses were performed in the prospectively identified inferential analysis set (IAS), comprised of the first 60 subjects in Cohort 1 to be infused with KTE-X19 and have the opportunity to be followed for at least six months after their first objective disease response. A CR or PR was observed in 52 of these 60 subjects, giving an ORR of 87% (95% CI 75.4 – 94.1), which included CRs in 37 (62%) of the subjects. With a median follow-up from date of first response of 240 days (range 0 to 888 days; 0 was the result of new anti-cancer therapy initiation following first disease response) prior to the 24 July 2019 data cutoff, the median DOR was not reached.

Based on review of the biologics license application (BLA) data summarized above while considering the nature of r/r MCL and the therapies available to this population, the clinical review team assesses a favorable risk-benefit profile based on overall response rates and duration of response and thus recommends accelerated approval of brexucabtagene autoleucel for the treatment of adult patients with r/r MCL. Accelerated approval may be considered for an agent that appears to address an unmet medical need based on an appropriate surrogate or intermediate endpoint reasonably likely to predict clinical benefit. Additional studies are performed to verify clinical benefit and support conversion to traditional approval. In this instance, favorable ORR with limited duration of follow-up serves as an intermediate endpoint reasonably likely to predict clinical benefit, with additional follow-up for response durability needed to verify clinical benefit.

In consideration of granting accelerated approval in a broader population of patients with r/r MCL than the population evaluated in ZUMA-2, the clinical team considered the following aspects:

1) The available therapies for patients with r/r MCL. Food and Drug Administration (FDA)-approved products under traditional approval were noted to have ORRs of 31% and CR rates of 8% at best. BTK inhibitors approved under accelerated approval demonstrated ORRs as high as 84%, CR rates as high as 50%, and median DOR of 19.5 months.
2) The available data in published literature for patients who had received prior anthracyclines or bendamustine and whose disease was r/r to BTK inhibitors to understand the unmet need. The limitations of the historical data, particularly with regard to bias, were noted and weighed in the context of the magnitude of benefit demonstrated by ORR and CR observed in ZUMA-2.
3) The observed magnitude of benefit observed in ZUMA-2 subjects, who likely represent a population in which attaining responses, particularly CRs, is more challenging than in the broader population.
4) Mechanistic actions of brexucabtagene autoleucel. There is no biological reason that predicts for decreased activity of the product in BTK inhibitor-naïve patients with r/r MCL as compared to BTK inhibitor-exposed patients with r/r MCL.

For additional details, please refer to 11.4 Recommendations on Regulatory Actions.

During the ZUMA-2 study, life-threatening adverse reactions attributed to KTE-X19 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 and fatal adverse reactions warrant warnings, including a boxed warning for cytokine release syndrome (CRS) and neurotoxicity, and a risk evaluation and mitigation strategy (REMS). FDA determined that a REMS with elements to assure safe use (ETASU) is necessary for KTE-X19. The foci of the REMS ETASU are site preparation, patient education, and risk mitigation strategies, with emphasis on early recognition and treatment of CRS and neurotoxicity. In order to minimize burden on the healthcare delivery system and because the YESCARTA REMS includes goals and ETASU identical to those necessary for the safe use of KTE-X19, a shared system REMS will encompass both drugs within a single REMS program.

Long-term safety after treatment with KTE-X19, particularly regarding the risk of insertional mutagenesis- related secondary malignancies, remains a concern due to the limited duration of follow-up. Therefore, a postmarketing requirement (PMR) safety study is warranted. 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 second malignancies. No routine collection of samples to evaluate for replication-competent retrovirus (RCR) is planned as part of this study.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

This application is based primarily upon data from ZUMA-2. Of the 122 patients who were screened, 91 enrolled on the study by undergoing leukapheresis, 84 were treated with conditioning chemotherapy, and 82 went on to receive any amount of KTE-X19. Of those 82, the median age was 63 years (range 38 to 79 years). Most subjects were white (75 of 82; 91%), male (68 of 82; 83%), of non-Hispanic or Latino ethnicity (67 of 82; 82%), and treated in the United States (76 of 82; 93%).

1.2 Patient Experience Data

Patient Experience Data Relevant to this Application

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☒	Patient reported outcome (PRO)	6.1.11.5 Exploratory and Post Hoc Analyses
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	

☐	Patient experience data was not submitted as part of this application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

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.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

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 r/r disease and has demonstrated objective response rates ranging from 71% to 92%, with complete response rates of 38% to 50%. Duration of response with this regimen was 19 months in a single arm study, while progression-free survival was 18 months in a randomized, controlled trial (5.5 Literature Reviewed references 18, 19, and 20). 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 (HCST) may lead to durable remission. However, allogeneic HSCT in particular comes with a high risk of treatment-related morbidity and 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 were 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. 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 (5.5 Literature Reviewed reference 7), and temsirolimus is not approved for any MCL indication in the United States.

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*

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)

2.3 Safety and Efficacy of Pharmacologically Related Products

KTE-X19 is the first chimeric antigen receptor (CAR) T cell product being developed for treatment of patients with mantle cell lymphoma; however, there are two FDA-approved CD19-directed CAR T cell products approved for other indications. Tisagenlecleucel treats children and young adults with r/r B cell precursor acute lymphoblastic leukemia, while both tisagenlecleucel and axicabtagene ciloleucel treat adults with r/r large B cell lymphoma. Additionally, multiple other anti-CD19 CAR T cell products are under clinical study to address a variety of medical needs. Clinical experience with these agents has revealed a distinct pattern of toxicity, including infections and cytopenias, but most notable for cytokine release syndrome and neurological toxicity.

Cytokine release syndrome (CRS) is a constellation of symptoms precipitated by cytokines and chemokines released from T cells upon their activation by engaging with target antigens. The hallmarks of CRS are fever, hypoxia, and hypotension, but patients may also experience malaise, fatigue, coagulation abnormalities, myalgias, and/or cardiac, renal, hepatic, or gastrointestinal toxicities. Symptom severity ranges from mild to life-threatening or fatal. Supportive care with intravenous (IV) fluids, supplemental oxygen, vasopressors, and endotracheal intubation and mechanical ventilation address the symptoms of CRS, while treatment with the IL-6 receptor monoclonal antibody tocilizumab works to control the underlying cytokine storm.

The immune effector cell-associated neurotoxicity syndrome (ICANS) is less well-characterized than CRS. Its pathophysiology remains a poorly defined area of active investigation. ICANS may present as headache, encephalopathy, confusion, somnolence, seizures, tremor, delirium, motor weakness, decreased level of consciousness, or cerebral edema, again running the gamut in severity from trivial to fatal. Most commonly, ICANS occurs in patients who also experience CRS, but it may

also occur independently. Corticosteroids are the mainstay of treatment, supplemented by sedatives and anti-epileptics.

Finally, there is a theoretical risk of secondary malignancy resulting from insertional mutagenesis in products modified with retroviral vectors. When gene therapies were first being developed, hematopoietic stem cells (HSCs) which had undergone retroviral transduction were transplanted into subjects with chronic granulomatous disease or severe combined immunodeficiency. T cell leukemias originating from insertional mutagenesis events were diagnosed in recipients of those therapies up to 15 years after infusion of the modified HSCs. Today's retrovirally transduced CAR T cell products are designed to proliferate following administration, and in some cases they may persist in the body for several years. As such, the theoretical possibility of insertional oncogenesis occurring remains.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Brexucabtagene autoleucel is a novel product with no prior human experience and has not been marketed in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

6 May 2015: ZUMA-2 originally submitted, as an amendment to KTE-C19 Investigational New Drug (IND) 16278.

28 April 2016: Orphan drug designation (ODD) granted to KTE-C19 for the treatment of MCL. 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 biologics license application (BLA) for KTE-X19.

16 September 2016: Manufacturing of the investigational product (IP) under study in ZUMA-2 changed from the KTE-C19 CLP process used to produce axicabtagene ciloleucel to the KTE-X19 XLP process to address the circulating tumor cells found in MCL. As a result, ZUMA-2 was re-filed under IND 16675.

15 June 2018: Breakthrough therapy designation (BTD) granted to KTE-X19 for the treatment of adults with r/r MCL.

25 September 2018: Initial multidisciplinary meeting held. Initial agreement on a primary endpoint for ZUMA-2 of objective response rate (ORR) per the 2014 Lugano Classification as determined by Independent Radiology Review Committee (IRRC) assessment of 60 subjects dosed at 2×10^6 anti-CD19 CAR T cells/kg with a minimum follow-up of six months after the Week 4 disease assessment, including 28 subjects followed for at least 24 months after the Week 4 disease assessment. Agreement reached on the definition of and censoring rules for duration of response (DOR) as found in the current protocol.

23 April 2019: FDA's pre-BLA format and content written responses sent. Primary efficacy endpoint revised to ORR per the 2014 Lugano Classification as determined by

IRRC assessment of the first 60 subjects dosed at 2 x 10^6 KTE-X19 cells/kg who have had the opportunity to be followed for at least six months after first objective response, in order to allow assessment of response durability.

24 September 2019: Pre-BLA risk evaluation and mitigation strategy (REMS) meeting held.

15 November 2019: Pre-BLA topline data meeting held. Agreement reached that the provided clinical data seemed acceptable to support a BLA submission.

11 December 2019: BLA submitted.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

ZUMA-2 is being conducted under IND 16675 in compliance with Good Clinical Practice. The Bioresearch Monitoring (BIMO) team elected to inspect MD Anderson Cancer Center, University of Rochester Medical Center, and Banner MD Anderson Cancer Center, none of which had been recently inspected. BIMO's selections were based on the sites' relatively high numbers of enrolled subjects, financial disclosures, and preliminary data review.

3.3 Financial Disclosures

Covered clinical study (name and/or number): ZUMA-2		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 580; 39 principal investigators, 541 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 13 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 9		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Nine principal investigators, one former principal investigator, and three sub-investigators each disclosed total payments greater than (b) (4) from advisory board fees, consultant fees, speaker fees, and/or a research agreement. Four disclosures exceeded (b) (4) Potential bias in efficacy results introduced by these payments was minimized through use of an Independent Radiology Review Committee (IRRC) for primary efficacy analysis, as well as an evaluation of concordance between IRRC and investigator assessments. To mitigate potential bias in safety data, including laboratory test results, site monitors verified source documentation and evaluated for both over- and under-reporting.

Nine sub-investigators under five principal investigators required certification of due diligence. In each instance, the sub-investigator left the study site before submitting complete financial disclosure information. The applicant searched payment and employment records for each of the nine sub-investigators and found no disclosable financial interests and/or arrangements according to 21 Code of Federal Regulations (CFR) Part 54.4(a)(3).

Clinical reviewer comment
The applicant employed appropriate risk-reduction strategies to minimize bias and investigated individuals who did not provide financial disclosure information. Neither the disclosed significant payments nor the missing disclosures are likely to have negatively impacted the integrity of ZUMA-2's conduct or findings.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Brexucabtagene autoleucel (KTE-X19) is a CD19-directed, genetically modified, autologous T cell immunotherapy. To prepare KTE-X19, a patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction to express a chimeric antigen receptor (CAR) comprising an anti-CD19 single chain variable fragment linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back in to the patient, where they can recognize and eliminate CD19-expressing target cells.

4.2 Assay Validation

Per FDA's chemistry, manufacturing, and controls reviewer, the assays that were utilized for KTE-X19 manufacturing and cell persistence determination were validated.

4.3 Nonclinical Pharmacology/Toxicology

Per FDA's pharmacology and toxicology reviewer, no carcinogenicity or genotoxicity studies have been conducted with KTE-X19.

4.4 Clinical Pharmacology

The clinical pharmacology of KTE-X19 was evaluated separately by two review teams: clinical pharmacology and pharmacometrics. Please see their full reviews for details.

4.4.1 Mechanism of Action

KTE-X19 is a CD19-directed, genetically modified, autologous T cell immunotherapy which binds to CD19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

4.4.2 Human Pharmacodynamics (PD)

Per FDA's clinical pharmacology reviewer, pharmacodynamic responses to KTE-X19 were evaluated over a four-week period by measuring levels of cytokines, chemokines, and other molecules in peripheral blood. Analytes included IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα. Peak elevation was generally observed between four and eight days after KTE-X19 infusion, and levels generally returned to baseline within 28 days.

4.4.3 Human Pharmacokinetics (PK)

Per FDA's clinical pharmacology reviewer, following infusion (target dose of 2×10^6 anti-CD19 CAR T cells/kg) of KTE-X19, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by three months. Peak levels of anti-CD19 CAR T cells occurred within the first seven to 15 days after KTE-X19 infusion.

The number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR). The median peak anti-CD19 CAR T cell level in responders was 102 cells/μL (range 0 to 2589 cells/μL; n = 52), and in non-responders was 12 cells/μL (range 0 to 1364 cells/μL; n = 8). The median $AUC_{Day\ 0\text{-}28}$ in subjects with an objective response was 1487 cells/μL•days (range 4 to 3E+04 cells/μL•days; n = 52) versus 169 cells/μL•days in non-responders (range: 2 to 1E+04 cells/μL•days; n = 8).

Median peak anti-CD19 CAR T cell values were 74 cells/μL in subjects >/= 65 years of age (n = 39) and 112 cells/μL in subjects < 65 years of age (n = 28). Median anti-CD19 CAR T cell $AUC_{Day\ 0\text{-}28}$ values were 876 cells/μL•day in subjects >/= 65 years of age and 1640 cells/μL•day in subjects < 65 years of age. Gender had no significant impact on $AUC_{Day\ 0\text{-}28}$ or C_{max} of KTE-X19.

Hepatic and renal impairment studies of KTE-X19 were not conducted.

4.5 Statistical

FDA's statistical reviewer verified that the key ZUMA-2 endpoint analyses reported by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

The available safety data suggest that a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is indicated, and the applicant has been notified. The recommendation for REMS is to ensure that the benefits of KTE-X19 outweigh the risks of CRS and neurotoxicity. The REMS should include ETASU to train health care providers, pharmacies, and prescribers and provide CRS and neurotoxicity-related risk mitigation measures as follows:

For hospitals:

1. To become certified to dispense KTE-X19, hospitals must:
    a. Designate an authorized representative to complete the certification process by submitting a completed KTE-X19 REMS Program Hospital Enrollment Form on behalf of the hospital.
    b. Ensure the authorized representative is assigned to the program for KTE-X19 and oversees implementation and compliance with the KTE-X19 REMS Program requirements by the following:
        i. Complete the training and successfully complete a KTE-X19 REMS Program Knowledge Assessment.
        ii. Ensure all relevant staff involved in the prescribing, dispensing, or administering of KTE-X19 are trained on the REMS Program requirements as described in the training materials, successfully complete a KTE-X19 REMS Program Knowledge Assessment, and maintain a record of training.
        iii. Goals of the training include: Informing prescribers and other staff about the risks, clinical manifestations, and management of CRS and neurotoxicity observed with KTE-X19 treatment.
    c. Put processes and procedures in place to ensure the following requirements are completed prior to dispensing and administering KTE-X19:
        i. Verify tocilizumab (two doses) is ordered and available for administration before a dose of KTE-X19 is administered.
        ii. Ensure that, during a pre-specified time period after product administration, procedures are in place to monitor patients at

the certified healthcare facility daily for at least seven days following infusion of KTE-X19 for signs and symptoms of CRS and neurologic events. Patients should also be informed of the importance of remaining close to the administering certified hospital for a pre-specified period of time (i.e., three to four weeks) so they can return if they develop symptoms of CRS or neurotoxicity.

iii. Ensure that the patient and family are given wallet cards to remind them of the signs and symptoms of CRS and neurotoxicity that require immediate medical attention.

2. As a condition of certification, the certified hospital must:
   a. Recertify in the KTE-X19 REMS Program if the hospital designates a new authorized representative. Procedures for routine re-education of all staff should be included in the REMS plan.
   b. Report any adverse events suggestive of CRS or neurotoxicity.
   c. Maintain documentation that all processes and procedures are in place and are being followed for the KTE-X19 REMS Program, and provide this documentation upon request to the applicant, FDA, or a third party acting on behalf of the applicant or FDA.
   d. Comply with audits by the applicant, FDA, or a third party acting on behalf of the applicant or FDA to ensure that all processes and procedures are in place and are being followed for the KTE-X19 REMS Program.
   e. Dispense KTE-X19 to patients only after verifying that two doses of tocilizumab are available for each patient and ready for administration within two hours.

For the applicant:

3. To implement KTE-X19 REMS Program in hospitals, the applicant must:
   a. Ensure that hospitals that dispense KTE-X19 are certified, in accordance with the requirements described above.
   b. Provide interactive training (either in person or via live webcast) for healthcare providers who prescribe, dispense, or administer brexucabtagene autoleucel to ensure that the hospital can complete the certification process. Provide all the following mechanisms for hospitals to complete: enrollment, documentation of training, knowledge assessment, and certification. The KTE-X19 REMS Program should include a procedure for recertifying hospitals.
   c. Ensure that hospitals are notified when they have been certified by the KTE-X19 REMS Program.
   d. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the certified hospital. If different, the hospital must be required to re-certify with a new authorized representative.

e. Provide the REMS materials listed below to all healthcare providers at new sites who: (1) attempt to order KTE-X19 and are not yet certified or (2) inquire about how to become certified:
    - KTE-X19 REMS Program Knowledge Assessment
    - Slides for Live Training / Hospital Training material(s)
    - KTE-X19 REMS Program Hospital Enrollment Form
    - KTE-X19 REMS Program website
    - KTE-X19 Patient Wallet Card
    - KTE-X19 Adverse Reaction Guide

4. To further implement the KTE-X19 REMS Program, the applicant must:
    a. Ensure that KTE-X19 is only distributed to certified hospitals.
    b. Maintain a validated secure database of hospitals that are certified to dispense KTE-X 19 in the KTE-X19 REMS Program.
    c. Maintain records of brexucabtagene autoleucel distribution and dispensing to certified hospitals to meet the REMS requirements.
    d. Maintain a KTE-X19 REMS Program Call Center and a REMS Program Website. The REMS Program Website must include the option to print the Package Insert, patient-directed labeling (Medication Guide), and KTE-X19 REMS materials. The KTE-X19 product website must include a prominent REMS-specific link to the KTE-X19 REMS Program Website. The KTE-X19 REMS website must not link back to the product website(s).
    e. Ensure that the KTE-X19 REMS Program website is fully operational, and the REMS materials listed in or appended to the KTE-X19 REMS document are available through the brexucabtagene autoleucel REMS Program Website and by calling the KTE-X19 REMS Program Call Center.
    f. Monitor that the certified hospitals are evaluating their training program on a regular basis to ensure the requirements of the KTE-X19 REMS Program are being met; institute corrective action if noncompliance is identified, and decertify hospitals that do not maintain compliance with the REMS requirements.
    g. Maintain, with certified hospitals, an ongoing annual audit plan, and audit all newly certified hospitals within 180 calendar days after the hospital places its first order for KTE-X19 to ensure that all processes and procedures are in place and functioning to support the requirements of the KTE-X19 REMS Program. The newly certified hospital must also be included in the applicant's ongoing annual audit plan.
    h. Take reasonable steps to improve implementation of and compliance with the requirements in the KTE-X19 REMS Program based on monitoring and evaluation of this program.

The pharmacovigilance plan includes a long-term, prospective, non-interventional registry study in patients treated with KTE-X19. This PMR study will follow the

recipients of KTE-X19 for 15 years to assess RCR, product persistence, and the potential for insertional mutagenesis that arises from KTE-X19's transduction with a retrovirus and results in an associated risk of secondary malignancy.

Clinical reviewer comments
The REMS with ETASU and the PMR safety study are the recommendation of the clinical review team with concurrence from the pharmacovigilance reviewers from the Center for Biologics Evaluation and Research (CBER) Office of Biostatistics and Epidemiology (OBE), Center for Drug Evaluation and Research (CDER) Division of Risk Management (DRISK), and the CBER Safety Working Group. The goal of the REMS is to ensure that sites are prepared for the safety risks of KTE-X19 that were identified in the IND phase of product development. The PMR registry study addresses the theoretical concerns of insertional mutagenesis and/or the development of a KTE-X19- related secondary malignancy. The applicant is proposing to enroll approximately 500 patients and follow each for 15 years; the final sample size is under review.

The clinical review team recommends that the label inform of the requirement to monitor patients at the certified healthcare facility daily for at least seven days following infusion of KTE-X19 for signs and symptoms of CRS and neurologic events. This recommendation is based on the requirements in the protocol, the clinical data related to the timing of onset of neurological and CRS events, and the availability of guidance to treat these serious adverse events. This recommendation is a reversal from the one given during approval of the first product for the applicant (YESCARTA©). The knowledge of and experience with CAR products has expanded over the intervening years, and with adequate safety procedures in place, outpatient monitoring is considered acceptable after brexucabtagene autoleucel infusion.

Negotiations with the applicant are ongoing regarding the final REMS and ETASU documents. Please refer to the action letter for final wording of the PMR.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The review of clinical efficacy was based upon ZUMA-2's study reports, case report forms, and submitted data, in addition to multiple information requests. Primary efficacy analyses were verified, and exploratory analyses were conducted, using JMP 15.

The clinical safety review was primarily based upon analysis of ZUMA-2 (KTE-102-C19), with a data cutoff date of 24 July 2019. The ZUMA-2 protocol design is described in 6.1.2 Design Overview. Subjects' characteristics and treatment regimens were similar between Cohort 1 and Cohort 2; the safety analysis of ZUMA-2 included both cohorts.

Supportive data from ZUMA-2 were used in the Integrated Summary of Safety (ISS) analysis. Data from ZUMA-3, ZUMA-4, and ZUMA-8 (see 5.3 Table of Studies/Clinical Trials for details of these studies) were reviewed but were not included in the ISS analysis, given the differences in patient population. ZUMA-3 and ZUMA-4 included subjects with acute lymphoblastic leukemia (ALL), a population predisposed to competing

adverse events from disease (refer to Table 3 in 5.3 Table of Studies/Clinical Trials for details).

The database lock for the 120-day safety update report (SUR) was 12 March 2020. The primary safety review was based on the originally-submitted data with a cutoff date of 24 July 2019. Key findings from the SUR are provided at the end of 6.1.12.6 Clinical Test Results.

The following subsections were omitted from this review because they do not apply to this application:

- 2.6 Other Relevant Background Information
- 5.4 Consultations
- 6.1.11.4 Dropouts and/or Discontinuations
- 7.1.1 Methods of Integration
- 7.1.2 Demographics and Baseline Characteristics
- 7.1.3 Subject Disposition
- 7.1.4 Analysis of Primary Endpoint(s)
- 7.1.5 Analysis of Secondary Endpoint(s)
- 7.1.6 Other Endpoints
- 7.1.7 Subpopulations
- 7.1.8 Persistence of Efficacy
- 7.1.10 Additional Efficacy Issues/Analyses
- 8.4.5 Clinical Test Results
- 8.4.7 Local Reactogenicity
- 8.5.4 Product-Disease Interactions
- 8.5.5 Product-Product Interactions
- 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
- 8.5.9 Person-to-Person Transmission, Shedding
- 9.1.4 Immunocompromised Patients
- 9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

See 5.1 Review Strategy.

5.3 Table of Studies/Clinical Trials

ZUMA-2 provides the basis for the efficacy and safety reviews and is summarized in Table 2. Safety analyses were primarily based on ZUMA-2, with supporting data from ZUMA-3, ZUMA-4, and ZUMA-8. The latter three studies are summarized in Table 3.

Table 2. Overview of primary study.

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
KTE-C19-102 (ZUMA-2)	Single arm, open-label, multicenter Phase 2 study of KTE-C19 or KTE-X19* infusion (~2 x 10^6 cells/kg) after Flu/Cy conditioning	Age >/= 18 years with relapsed/refractory mantle cell lymphoma (MCL)	ORR per IRC investigator	Cohort 1 74 apheresed 68 treated Cohort 2 17 apheresed 14 treated	24 July 2019

Flu/Cy = fludarabine and cyclophosphamide

**Both KTE-C19 and KTE-X19 are composed of anti-CD19 CAR T cells; the products differ in their manufacturing processes. In ZUMA-2, the first ten subjects were treated with KTE-C19, and all others with KTE-X19.*

Table 3. Overview of supportive studies providing additional safety data.

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
KTE-C19-103 (ZUMA-3)	Single arm, open-label, multicenter Phase 1/2 study of KTE-X19 infusion (~0.5, 1, or 2 x 10^6 cells/kg) after Flu/Cy conditioning	Age >/= 18 years with relapsed/refractory adult B cell precursor acute lymphoblastic leukemia (ALL)		12 apheresed 11 treated	26 June 2019
KTE-C19-104 (ZUMA-4)	Single arm, open-label, multicenter Phase 1/2 study of KTE-X19 infusion (~1 or 2 x 10^6 cells/kg) after Flu/Cy conditioning	Age 2-21 years with relapsed/refractory pediatric B cell precursor acute lymphoblastic leukemia (ALL)		5 apheresed 4 treated	26 June 2019
KTE-C19-108 (ZUMA-8)	Single arm, open-label, multicenter Phase 1/2 study of KTE-X19 infusion (~0.5, 1 or 2 x 10^6 cells/kg) after Flu/Cy conditioning	Age >/= 18 years with relapsed/refractory chronic lymphocytic leukemia (CLL)		7 apheresed 5 treated	26June 2019

Flu/Cy = fludarabine and cyclophosphamide

5.5 Literature Reviewed

1. Acalabrutinib prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf.
2. Bortezomib prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf.
3. Cheah CY, Chihara D, et al. Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. *Annals of Oncology* 2015;26:1175-1179.
4. Cheson BD, Fisher RI, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol* 2014;32(27):3059-3067.
5. Cheson BD, Pfistner B, et al. Revised Response Criteria for Malignant Lymphoma. *J Clin Oncol* 2007;25(5):579-586.
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7. Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomized, open-label, phase 3 study. *Lancet* 2016;387(10020):770-778.
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9. Eyre TA, Walter HS, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. *Haematologica*. 2019;104(2):e68-e71.
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13. Jain P and Wang M. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. *Am J Hematol* 2019;94:710-725.
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15. Lahda A, Zhao J, et al. Mantle cell lymphoma and its management: where are we now? *Exp Hematol Oncol* 2019;8:2-10.
16. Lenalidomide prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021880s057lbl.pdf.

17. McCulloch R, Visco C, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. *British Journal of Haematology* 2020;189:684-688.
18. Robinson KS, Williams ME, et al. Phase II Multicenter Study of Bendamustine Plus Rituximab in Patients With Relapsed Indolent B-cell and Mantle Cell non-Hodgkin's Lymphoma. *J Clin Oncol* 2008;26(27):4473-4479.
19. Rummel M, Atta J, Welslau M. Bendamustine and rituximab (BR) is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol* 2005;23:3383-3389.
20. Rummel M, Kaiser U, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicenter, randomized, open-label, non-inferiority phase 3 trial. *Lancet Oncol* 2016;17:57-66.
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25. Zanubrutinib prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.
26. Zelenetz AD, Gordon LI, et al. Non-Hodgkin's Lymphomas, Version 4.2014: Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2014;12(9):1282-1303.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Study identification codes

- Study number KTE-C19-102
- IND number 16675
- EudraCT number 2015-005008-27
- ClinicalTrials.gov identifier NCT02601313

Study title: A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)

6.1.1 Objectives (Primary, Secondary, etc)

Primary objective: Evaluate the efficacy of KTE-X19, as measured by objective response rate (ORR), in subjects with relapsed/refractory (r/r) mantle cell lymphoma (MCL)

Secondary objectives
Assess:

- The safety and tolerability of KTE-X19
- Additional efficacy endpoints
- The change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6

6.1.2 Design Overview

ZUMA-2 is an ongoing single arm, Phase 2, multicenter, international, open-label study of KTE-X19's safety and efficacy in the treatment of adults with r/r MCL. The study opened on 16 May 2016, with data cutoff for this BLA on 24 July 2019.

6.1.3 Population

Adults with pathologically confirmed r/r MCL were eligible to enroll after receipt of up to five prior MCL-directed lines of treatment, which must have included:

- A chemotherapy regimen containing bendamustine or an anthracycline,
- An anti-CD20 antibody, and
- A Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib and/or acalabrutinib)

To enroll, patients must additionally have had:

- Measurable disease
- No central nervous system (CNS) lymphoma on magnetic resonance imaging
- Completed at least two weeks' or five half-lives' washout from systemic therapy (except at least three half-lives' washout from immune checkpoint therapy) at the time of leukapheresis
- Any clinically significant toxicities from prior therapies stable or recovered to </= Grade 1
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Absolute neutrophil count >/= 1,000/uL
- Platelet count >/= 75,000/uL
- Absolute lymphocyte count >/= 100/uL
- Cockcroft-Gault creatinine clearance >/= 60 mL/min
- Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) </= 2.5 times the upper limit of normal (x ULN)
- Total bilirubin </= 1.5 mg/dL, except in those with Gilbert syndrome
- By echocardiogram, cardiac ejection fraction >/= 50% and no evidence of pericardial effusion

Patients may not have had or been:

- Prior allogeneic HSCT (alloHSCT)
- Prior CD19-targeted therapy
- Prior genetically modified T cell therapy, including CAR T cells
- History of human immunodeficiency virus (HIV) infection

- Active or uncleared hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
- History of or currently present CNS disorder
- Clinically significant cardiac disease, including active arrhythmias, within the prior 12 months

6.1.4 Study Treatments or Agents Mandated by the Protocol

Leukapheresis

- Within five days of confirming study eligibility
- 12- to 15-liter apheresis targeting collection of 5 to 10 x 10^9 mononuclear cells

Bridging therapy

- Per investigator's discretion after discussion with the medical monitor
- Initiated after leukapheresis and completed at least five days prior to beginning conditioning chemotherapy
- Acceptable regimens:
    - Dexamethasone 20 to 40 mg or equivalent, orally (*per os*; PO) or intravenously (IV) daily for one to four days
    - Ibrutinib 560 mg PO daily, or most recent dose if there had been a dose adjustment
    - Acalabrutinib 100 mg PO every 12 hours, or most recent dose if there had been a dose adjustment
- Corticosteroid agent and dose could be adjusted for age, comorbidities, or per local or institutional guidelines

Clinical reviewer comment
Among the inferential analysis set (n = 60), subjects received the following bridging therapies:

- *Any: 21 (35%)*
- *Corticosteroids*
    - *Any: 9 (15%)*
    - *Dexamethasone only: 7 (12%)*
    - *Dexamethasone plus methylprednisolone: 2 (3%)*
- *BTK inhibitors*
    - *Any: 16 (27%)*
    - *Acalabrutinib: 5 (8%)*
    - *Ibrutinib: 11 (18%)*
- *Both a corticosteroid and a BTK inhibitor: 4 (7%)*

Lymphodepleting, non-myeloablative conditioning chemotherapy

- Day -5, Day -4, and Day -3 prior to KTE-X19 infusion
- On each of the three days, administer:
    - One liter 0.9% sodium chloride (NaCl) IV, then
    - Cyclophosphamide 500 mg/m^2 IV over approximately 60 minutes, then
    - Fludarabine 30 mg/m^2 IV over approximately 30 minutes, and
    - One liter 0.9% NaCl IV (upon completion of cyclophosphamide infusion)
- Cyclophosphamide hydration could be performed according to local institutional guidelines
- Add mesna according to local institutional guidelines

Clinical reviewer comments
Fifty-three (88%) of the 60 inferential analysis set subjects received conditioning chemotherapy per protocol. One subject (2%) was treated with the three doses of cyclophosphamide and three doses of fludarabine over six days rather than the protocol-defined three days, followed by KTE-X19 administration five days later rather than the protocol-defined three days later. An additional six (10%) subjects experienced a delay between completing lymphodepletion and receiving KTE-X19 infusion, with total intervals of four [one subject (2%)], five [one subject (2%)], seven [three subjects (5%)], and ten [one subject (2%)] days. This small proportion of generally minor deviations is unlikely to have influenced the key study results.

KTE-X19

- Day 0
- Approximately one hour prior to KTE-X19 infusion, administer:
  - Acetaminophen 650 mg PO
  - Diphenhydramine 12.5 to 25 mg IV or 25 mg PO
- Administer KTE-X19 as a single IV infusion
  - Target dose 2 x 10^6 anti-CD19 CAR T cells/kg
  - Minimum dose (b) (4) anti-CD19 CAR T cells/kg
  - Maximum dose 2 x 10^8 anti-CD19 CAR T cells

Clinical reviewer comments
Premedication was administered per protocol to 19 (32%) of the 60 inferential analysis set subjects. The remaining 41 (68%) were treated with a variety of different doses, alternative routes, partial premedication, or no premedication. This likely reflects the variation in premedication practices between institutions and among providers and is unlikely to have influenced the key study results despite the high rate of protocol non-adherence.

All KTE-X19 doses administered to the 60 inferential analysis set subjects were within the specified range. Most (54; 90%) subjects were infused with the target dose, 2 x 10^6 anti-CD19 CAR T cells/kg. One subject (2%) received 1 x 10^6 anti-CD19 CAR T cells/kg, one (2%) received 1.6 x 10^6 anti-CD19 CAR T cells/kg, two (3%) received 1.8 x 10^6 anti-CD19 CAR T cells/kg, and two (3%) received 1.9 x 10^6 anti-CD19 CAR T cells/kg. The number of subjects given fewer than 2 x 10^6 anti-CD19 CAR T-cells/kg and the degree of deviation from this goal are unlikely to have significantly altered the primary study outcomes. Please see 6.1.11.5 Exploratory and Post Hoc Analyses for further details.

6.1.5 Directions for Use

KTE-X19 was supplied cryopreserved in cryostorage bags, labelled with a unique subject identification number, to be stored in the vapor phase of liquid nitrogen until the subject was prepared for treatment. At that time, the product was thawed and infused. Instructions regarding storage and administration of KTE-X19 were detailed in the Investigational Product Manual.

6.1.6 Sites and Centers

United States

- H. Lee Moffitt Cancer Center
- MD Anderson Cancer Center
- Henry-Joyce Cancer Clinic
- The Sarah Cannon Research Institute
- Colorado Blood Cancer Institute
- Hackensack University Medical Center
- University of Rochester Medical Center
- Barbara Ann Karmanos Cancer Institute
- Cleveland Clinic Foundation
- Dana-Farber Cancer Institute
- Banner MD Anderson Cancer Center
- Sylvester Comprehensive Cancer Center
- Ronald Reagan University of California—Los Angeles Medical Center
- Stanford University Medical Center
- Duke Cancer Center
- Emory University Hospital
- Baylor University Medical Center
- Swedish Cancer Institute
- Temple Bone Marrow Transplant Program
- James Cancer Hospital and Solove Research Institute at The Ohio State University Comprehensive Cancer Center

The Netherlands

- Universiteit Van Amsterdam—Academisch Medisch Centrum

France

- Hopital Saint Louis
- Hopital Haut Leveque

Germany

- Universitaetsklinik Wuerzburd Medizinische Klinik und Poliklinik II

Clinical reviewer comment
After consideration of factors including subject enrollment and outcomes, protocol deviations, financial disclosures, geographic location, and inspection history, three clinical sites were selected for inspection and verification of submitted data by FDA's Bioresearch Monitoring (BIMO) team: MD Anderson Cancer Center, University of Rochester Medical Center, and Banner MD Anderson Cancer Center. Review of site records of the six subjects enrolled at the University of Rochester Medical Center revealed changes to investigators' reported disease response assessments at one timepoint for each of three (50%) subjects, without documented justification. FDA's clinical team found that the submitted data were adequate to verify the final disease response determinations for each of the three subjects. There were no significant findings during the BIMO inspections, and no follow-up action was indicated. For additional details, please see the BIMO review memorandum.

6.1.7 Surveillance/Monitoring

Table 4. ZUMA-2 schedule of assessments from Screening through Month 3 of Post-treatment Follow-up.

Procedures	Screening	Enrollment/ Leukapheresis	Bridging Therapy Period	Conditioning Chemotherapy Period					IP Administration Period[a]		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	Within 28 days of enrollment	Within approx. 5 days after eligibility confirmation	Completed within 5 days prior to conditioning chemotherapy	-5	-4	-3	-2	-1	0	1 - 7	Week 2 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Medical history	X													
ECOG performance status	X													
EQ-5D questionnaire	X											X		X
Neurological assessment including MMSE[b] for Cohort 1	X								X	QOD		X		X
Neurological assessment including MMSE[c] for Cohort 2	X											X		X
ECG	X													
ECHO	X													
Archival/fresh tumor to central laboratory[d]		X								between Day 7 & Day 14				
Brain MRI	X													
PET-CT/ disease assessment[e]	X		X									X		X
Bone marrow assessment[f]	X											X		X
Physical exam	X										X	X	X	X
Vital signs (BP, HR, O_2 sat, temp)	X	X	X	X	X	X			X	X	X	X	X	X
Weight (plus height at screening)	X	X												
Pregnancy test (serum or urine)	X													X
Lumbar puncture[g]	X									X				
Blood draw for chemistry panel with CRP	X	X		X	X	X			X	X	X	X	X	X
Blood draw for CBC with differential	X	X		X	X	X			X	X	X	X	X	X
Blood draw for anti-CD19 CAR antibody[h]		X										X		X
Blood draw for PBMCs[i,j]		X							X	Day 7	X	X		X
Blood draw for cytokines[j]		X							X	Day 3 & 7	X	X		
Leukapheresis		X												

Procedures	Screening	Enrollment/ Leukapheresis	Bridging Therapy Period	Conditioning Chemotherapy Period					IP Administration Period[a]		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	Within 28 days of enrollment	Within approx. 5 days after eligibility confirmation	Completed within 5 days prior to conditioning chemotherapy	-5	-4	-3	-2	-1	0	1 - 7	Week 2 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Bridging therapy (if applicable)			X											
Fludarabine/cyclophosphamide				X	X	X								
KTE-X19 infusion IV									X					
Adverse events/ Concomitant medications	X	→	→	→	→	→	→	→	→	→	→	→	→	→

Abbreviations: AE, adverse event; approx, approximate; BP, blood pressure; CAR, chimeric antigen receptor; CBC, complete blood count; CNS, central nervous system; CR, complete response; CRP, C-reactive protein; CSF, cerebrospinal fluid; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life-5 Dimensions; FFPE, formalin-fixed paraffin-embedded; HR, heart rate; IP, investigational product; IV, intravenous; MMSE, Mini-Mental State Exam; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; PET-CT, positron emission tomography-computed tomography; PBMC, peripheral blood mononuclear cell; QOD, every other day; RCR, replication competent retrovirus; SAE, serious adverse event; Sat, saturation; Temp, temperature.

a Refer to the protocol (Appendix 16.1.1 Protocol Amendment 6, Section 18.3) for requirements by country regulatory agencies.
b MMSE: Subjects enrolled in Cohort 1 were to have the MMSE assessment at screening, before KTE-X19 administration on Day 0, every other day through hospitalization, on Day 28, and at Month 3.
c MMSE: Subjects enrolled in Cohort 2 were to have the MMSE assessments at screening and on Day 28. If the assessment had not returned to baseline (± 3 points) on Day 28, then the MMSE was to be performed at Month 3 and every 3 months until the results had returned to baseline (± 3 points) or until Month 24
d Archival/fresh tumor sample: Either FFPE tumor block or up to 20 unstained slides. A fresh tumor sample was to be obtained from subjects who signed the optional portion of the consent form. Archived and fresh tumor samples (if applicable) were to be submitted to the central laboratory after eligibility had been confirmed and prior to the start of conditioning chemotherapy. Post-treatment fresh tumor samples (if applicable) were to be collected/submitted anytime between Day 7 and Day 14.
e PET-CT (neck-chest-abdomen-pelvis)/disease assessment: If PET-CT was performed > 28 days prior to the initiation of conditioning chemotherapy, baseline scans must have been repeated. Screening PET-CT scans were to be completed as close to enrollment as possible. A repeat baseline PET-CT was required after bridging therapy and prior to conditioning chemotherapy.
f Bone marrow assessment: Bone marrow aspirate/biopsy as needed (if not done within 4 weeks before screening). As applicable, bone marrow aspirate/biopsy was to be performed to confirm CR (ie, for subjects presenting with bone marrow involvement prior to therapy, or if new abnormalities in the peripheral blood counts or blood smear caused clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples could also be collected for subjects who developed toxicities after KTE-X19 infusion; these samples were to be analyzed centrally. A repeat bone marrow biopsy (if applicable) was required after bridging therapy and prior to conditioning chemotherapy. After CR was confirmed by bone marrow biopsy, additional bone marrow biopsies were only required in case of clinical suspicion of disease progression that was limited to the bone marrow.
g Lumbar puncture: Subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) were to have lumbar puncture performed at screening to assess CSF for possible CNS involvement. Subjects with new onset Grade 2 or higher neurologic symptoms after KTE-X19 infusion were to have lumbar puncture performed to assess CSF. In addition, subjects who signed the optional portion of the consent form were to have a lumbar puncture performed for the collection of CSF at baseline prior to KTE-X19 infusion and following infusion (Day 5 ± 3 days).
h Blood draw for immunogenicity testing: Baseline antibody samples were to be collected prior to the start of conditioning chemotherapy. For immunogenicity testing after Month 3, see Appendix 16.1.1 Protocol Amendment 6, Section 7.11.
i PBMCs: Blood draw for PBMCs included the analysis of lymphocytes, anti-CD19 CAR T cells, and RCR.
j If a subject were subsequently re-admitted to the hospital with any KTE-X19-related AEs, blood samples for anti-CD19 CAR T cells and cytokines were to be collected on the day of admission, then weekly, and then on the day of discharge. Blood samples for anti-CD19 CAR T cells and cytokines were also to be collected at the time of disease progression.

(Source: Original BLA 125703/0.0, 5.3.5.2 Report Body, Table 2, pages 31-32 of 997)

Table 5. ZUMA-2 schedule of assessments during the Long-term Follow-up Period.

Procedure	Long-term Follow-up Period (Each visit calculated from Day 0)												
Visit Frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Thereafter**
EQ-5D questionnaire	X												
Neurological assessment including MMSE[a] for Cohort 2	X	X	X	X	X	X							
Physical exam[b]	X	X	X	X	X	X							
PET-CT Disease assessment[c]	X	X	X	X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Bone marrow assessment[d]	X	X	X	X	X	X							
Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential[e]	X	X	X	X	X	X							
Anti-CD19 CAR antibody[f]													
Blood draw for PBMCs[g]	X	X	X	X	X	X		X		X		X	X
Targeted AE/SAEs[h]	X	X	X	X	X	X							
Targeted concomitant medications[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for NHL[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Fresh tumor sample to central laboratory[k]	X												

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CBC, complete blood count; CR, complete response; CRP, C-reactive protein; EQ-5D, European Quality of Life-5 Dimensions; MMSE, Mini-Mental State Exam; NHL, non-Hodgkin lymphoma; PET-CT, positron emission tomography-computed tomography; PBMC, peripheral blood mononuclear cell; RCR, replication competent retrovirus; SAE, serious adverse event.

a MMSE: For subjects enrolled in Cohort 2, if the MMSE performed on Day 28 and Month 3 had not returned to baseline (± 3 points), then the MMSE was to be performed at Month 6 and every 3 months until the results had returned to baseline (± 3 points) or until Month 24, whichever occurred first.

b Physical exams were to continue through the first 24 months.

c PET Scans/disease assessments were to continue through Month 24 or until disease progression, whichever occurred first. If the subject's disease had not progressed by Month 24, disease assessments were to continue being performed per standard of care.

d Bone Marrow Assessment: As applicable, bone marrow aspirate/biopsy was to be performed to confirm CR (ie, for subjects who presented with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear caused clinical suspicion of bone marrow involvement with lymphoma after treatment). After CR was confirmed by bone marrow biopsy, additional bone marrow biopsies were only required in case of clinical suspicion of disease progression in the bone marrow only.

e Subjects were to continue to provide samples for CBC with differential and lymphocyte subsets through Month 24.

f For additional information regarding immunogenicity testing after Month 3, refer to Appendix 16.1.1 Protocol Amendment 6, Section 7.11.

g Blood draws for PBMCs were to be used for the analysis of lymphocytes, anti-CD19 CAR T cells, and RCR.

h Targeted AEs and SAEs were to be recorded for 24 months or until disease progression, whichever occurred first.

i Targeted concomitant medications were to be recorded for 24 months or until disease progression, whichever occurred first.

j Subsequent therapy administered after KTE-X19 infusion for a subject's disease, such as nonstudy-specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy, must have been recorded until the subject completed the long-term follow-up period, was considered lost to follow-up, withdrew consent, or died. Subjects could be contacted by telephone to collect information about subsequent therapy for NHL and to assess survival status.

k Fresh tumor samples were to be obtained from subjects who signed the optional portion of consent; refer to Appendix 16.1.1 Protocol Amendment 6, Section 7.11. for additional information.

(Source: Original BLA 125703/0.0, 5.3.5.2 Report Body, Table 2, page 33 of 997)

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: Objective response rate (ORR) as assessed centrally using the Lugano Classification (2014)

Secondary endpoints

- Subject incidence of each category of best objective response (BOR; CR, PR, stable disease [SD], progressive disease [PD], and not evaluable [NE]) using central assessment per the Lugano Classification (2014)
- ORR and subject incidence of each category of BOR using investigator assessment per the International Working Group (IWG) 2007 Criteria for Malignant Lymphoma
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)

Clinical reviewer comment
Central reviewers used different disease response assessment criteria than did investigators. ZUMA-2 opened in 2016 with site investigators, who were the only disease response assessors at that time, utilizing the IWG 2007 system. When central review began, the disease response assessment instrument was updated to the Lugano Classification. To maintain consistency, however, investigators continued using IWG 2007 throughout the study. The differing criteria did lead to some discrepancies but did not significantly change the study results [see 6.1.11.1 Analyses of Primary Endpoint(s) and 6.1.11.2 Analyses of Secondary Endpoints].

6.1.9 Statistical Considerations & Statistical Analysis Plan

ZUMA-2 tested the hypothesis that the objective response rate (ORR) after treatment with KTE-X19, as assessed by the Independent Radiology Review Committee, is significantly greater than 25%. It was assumed that the subjects' responses were independent and followed a binomial distribution. The primary analysis was performed after 60 subjects in Cohort 1 were treated with KTE-X19 and had the opportunity to be followed for at least six months after their first objective disease response; with a one-sided alpha level of 0.025, this provided at least 96% power to differentiate between a treatment with a true ORR of 50% and one of 25% or less. Pre-specified covariates for potential subgroup analyses included Eastern Cooperative Oncology Group (ECOG) performance status, age, sex, race, relapsed/refractory subgroup (either relapsed after autologous HSCT [autoHSCT], relapsed after last MCL therapy, or refractory to last MCL therapy), tumor morphology, Ki-67 index, presence of t(11;14), overexpression of cyclin D1, disease stage and extent, simplified MCL International Prognostic Index (s-MIPI), number of prior regimens, particular prior therapies (ibrutinib, acalabrutinib, anti-CD20 antibody, anthracycline, bendamustine, lenalidomide, bortezomib, temsirolimus, HSCT, platinum), tumor burden, and tocilizumab and/or steroid treatment after KTE-X19 infusion.

Key definitions:

- Safety

  - Treatment-emergent adverse event (TEAE): Any adverse event with onset during or after KTE-X19 infusion; to be summarized by preferred term and toxicity grade.
  - Adverse events of special interest (AESI): Previously identified risks of study treatment—cytokine release syndrome (CRS), neurologic events, cytopenias, infections, and hypogammaglobulinemia—as well as potential risks of study treatment—immunogenicity, secondary malignancies, replication-competent retrovirus (RCR), and tumor lysis syndrome (TLS).

- Efficacy
  - Objective response rate (ORR): The proportion of subjects with either a complete response (CR) or partial response (PR) while on study.
  - Duration of response (DOR): The time from first objective response to disease progression or death.
  - Progression-free survival (PFS): The time from KTE-X19 infusion to disease progression or death from any cause. For analyses of populations including subjects who were enrolled but not treated with KTE-X19, PFS was defined as the time from enrollment to disease progression or death from any cause.
  - Overall survival (OS): The time from KTE-X19 infusion to death from any cause. For analyses of populations including subjects who were enrolled but not treated with KTE-X19, OS was defined as the time from enrollment to death from any cause.

Key censoring rules:

- ORR, DOR, and PFS only include data from disease assessments performed prior to HSCT, retreatment with KTE-X19, or initiation of any other anti-cancer therapy.
- DOR and PFS: Subjects who received HSCT, retreatment with KTE-X19, or initiation of any other anti-cancer therapy were censored at their last evaluable disease assessment prior to the additional therapy. Subjects who had not died or experienced disease progression by the analysis cutoff date were censored at their last evaluable disease assessment.
- OS: Subjects who had not died by the analysis cutoff date were censored at their last date known alive or the analysis cutoff date, whichever was earlier.

Clinical reviewer comment
Please see the statistical review for further information.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Subject populations in ZUMA-2 were defined and analyzed as follows:

- Inferential analysis set (IAS): The first 60 subjects in Cohort 1 who were treated with KTE-X19. Used for hypothesis testing of the primary endpoint during the primary analysis as well as for efficacy analyses in Cohort 1.
- Safety analysis set (SAS): All subjects treated with any dose of KTE-X19. Used for safety analyses.

- Full analysis set (FAS): All subjects who were enrolled (defined as commencing leukapheresis) on ZUMA-2. Used for summary of subject disposition and analyses of ORR, BOR, DOR, PFS, and OS.
- Modified intent-to-treat analysis set (mITTAS): All subjects treated with any dose of KTE-X19. Identical to the safety analysis set.
- Subgroup analysis sets (SubAS): Subgroups defined by treatment with bridging therapy, receipt of tocilizumab and corticosteroids, or baseline covariates such as subject age or tumor morphology. Used for analyses of selected efficacy and safety endpoints.

6.1.10.1.1 Demographics

The inferential analysis set (IAS; n = 60) subjects had a median age of 65 years (range 38 to 79). These age statistics remain unchanged when considering all treated Cohort 1 subjects (n = 68) or all treated ZUMA-2 subjects [safety analysis set (SAS), n = 82]. Most subjects were white men treated in the United States, as described in Table 6.

Table 6. Demographic characteristics in ZUMA-2 (SAS, n = 82 and IAS, n = 60).

	SAS N (%)	**IAS N (%)**
All	82 (100%)	60 (100%)
Age Category		
< 65 Years	40 (49%)	28 (47%)
>/= 65 Years	42 (51%)	32 (53%)
Sex		
Female	14 (17%)	9 (15%)
Male	68 (83%)	51 (85%)
Race		
Black or African American	1 (1%)	1 (2%)
Native Hawaiian or Other Pacific Islander	1 (1%)	1 (2%)
Other	5 (6%)	2 (3%)
White	75 (91%)	56 (93%)
Ethnicity		
Hispanic or Latino	13 (16%)	10 (17%)
Not Hispanic or Latino	67 (82%)	48 (80%)
Unknown	2 (2%)	2 (3%)
Country of Treatment		
Germany	1 (1%)	0 (0%)
France	3 (4%)	0 (0%)
Netherlands	2 (2%)	1 (2%)
United States	76 (93%)	59 (98%)

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Data Analysis Data, dataset ADSL)

Clinical reviewer comments

Demographic characteristics (Table 6) are displayed for the safety analysis set (SAS) of all 82 subjects treated with KTE-X19 across both Cohort 1 and Cohort 2, as well as for the inferential analysis set (IAS) of the first 60 subjects in Cohort 1 treated with KTE-X19 and with the opportunity to be followed for at least six months after their first objective disease response. This is because primary safety analyses are based on the SAS, while primary efficacy analyses are based on the IAS. Additionally, displaying data from these two groups side by side facilitates comparison and demonstrates that the IAS was demographically similar to the treated study population as a whole. The population of all 91 leukapheresed subjects was also demographically similar to the SAS and IAS, suggesting that selection bias was not responsible for the subgroup of nine (10% of the 91 leukapheresed) subjects who were leukapheresed but not treated.

Overall, the study population appears representative of those with mantle cell lymphoma in the United States: median age in the mid-60s, with a predominance of males and Caucasians. As described in 2.1 Disease or Health-Related Condition(s) Studied, these are the expected observations for age, sex, and racial distribution.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
As detailed in 6.1.3 Population, eligibility criteria for enrollment on ZUMA-2 allowed up to five prior MCL-directed lines of therapy and required prior receipt of:

- Bendamustine- or anthracycline-containing chemotherapy,
- An anti-CD20 antibody, and
- Ibrutinib or acalabrutinib

The 60 subjects who comprised the inferential analysis set (IAS) had been treated with a median of three prior lines of therapy (range two to five). One subject (2% of 60) had not received either an anthracycline or bendamustine; otherwise, all 60 subjects met all prior therapy eligibility criteria. Fifty-two subjects (87% of 60) had previous exposure to ibrutinib, 14 (23% of 60) to acalabrutinib, and six (10% of 60) to both ibrutinib and acalabrutinib, with duration of exposure as detailed in Tables 7 and 8.

Table 7. Days of exposure to BTK inhibitors prior to ZUMA-2, all IAS subjects (IAS, n = 60).

	Ibrutinib	**Acalabrutinib**	**Any BTK Inhibitor**
Mean	307	50	357
Standard Deviation	333	118	340
Median	184	0	215
Minimum	0	0	1
Maximum	1512	503	1512

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Data Analysis Data, dataset ADCM)

Table 8. Days of exposure to BTK inhibitors prior to ZUMA-2, exposed IAS subjects only (IAS, n = 60).

	Received Any Ibrutinib (n = 52)	Received Any Acalabrutinib (n = 14)	Received Both Ibrutinib and Acalabrutinib (n = 6)
Mean	355	212	658
Standard Deviation	333	157	332
Median	227	153	630
Minimum	1	29	88
Maximum	1512	503	1133

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Data Analysis Data, dataset ADCM)

Clinical reviewer comment
Although technically meeting the prior exposure eligibility criteria, one subject (2% of 60) received only a single dose of ibrutinib one month prior to leukapheresis. Ibrutinib was discontinued due to "disease progression", and the subject was not treated with acalabrutinib. However, all other subjects had at least 29 days of BTK inhibitor exposure before enrolling on ZUMA-2.

Additional baseline tumor and subject status characteristics are detailed in Table 9. Roughly one-third of subjects had tumors with blastoid or pleomorphic histology, 43% had failed autoHSCT, and nearly two-thirds were refractory to their most recent prior line of MCL therapy.

Table 9. Baseline disease characteristics in ZUMA-2 (SAS, n = 82 and IAS, n = 60).

	SAS N (%)	IAS N (%)
All	82 (100%)	60 (100%)
ECOG Performance Status		
0	51 (62%)	39 (65%)
1	31 (38%)	21 (35%)
Tumor Morphology		
Blastoid	23 (28%)	14 (23%)
Classical MCL Other	6 (7%)	4 (7%)
Diffuse	24 (29%)	17 (28%)
Nodular	11 (13%)	10 (17%)
Other	2 (2%)	1 (2%)
Pleomorphic	6 (7%)	4 (7%)
Unknown	10 (12%)	10 (17%)
Disease Stage		
II	3 (4%)	2 (3%)
III	8 (10%)	8 (13%)
IV	71 (87%)	50 (83%)
s-MIPI Category		
High Risk	12 (15%)	8 (13%)
Intermediate Risk	33 (40%)	25 (42%)
Low Risk	34 (41%)	25 (42%)
Unknown	3 (4%)	2 (3%)
Ki-67 Index (Central)		
< 30%	11 (13%)	8 (13%)
>/= 30%	50 (61%)	38 (63%)
Unknown	21 (26%)	14 (23%)
Prior AutoHSCT		
Yes	35 (43%)	26 (43%)
No	47 (57%)	34 (57%)
Response to Last Prior Therapy		
Relapsed	26 (32%)	21 (35%)
Refractory	50 (61%)	36 (60%)
NE/Unknown	6 (7%)	3 (5%)

AutoHSCT = autologous hematopoietic stem cell transplant, ECOG = Eastern Cooperative Oncology Group, MCL = mantle cell lymphoma, NE = not evaluable, s-MIPI = simplified Mantle Cell Lymphoma International Prognostic Index

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Data Analysis Data, dataset ADBASE)

Clinical reviewer comments

As with the demographic information in Table 6 (6.1.10.1 Populations Enrolled/Analyzed), Table 9 shows baseline disease characteristics for both the SAS (n

= 82) and the IAS (n = 60) to improve understanding of safety and efficacy analysis results and allow comparison of the two groups. Again, the two populations are similar to each other and to the larger group of all 91 leukapheresed subjects.

Thirteen percent of the IAS were classified as high risk according to the simplified Mantle Cell Lymphoma International Prognostic Index (s-MIPI). This is a similar proportion to that observed in the study populations upon which accelerated approval of two of the three most recent agents intended to treat r/r MCL were based (13% of zanubrutinib subjects had a high risk MIPI; 17% of acalabrutinib subjects had a high risk s-MIPI), but less than that of the third agent's study population (49% of ibrutinib subjects had a high risk s-MIPI). S-MIPI has validated prognostic value at the time of MCL diagnosis. However, its utility in relapsed or refractory disease has not been established, so it cannot support sound clinical conclusions.

Of the 60 IAS subjects tested centrally, 38 (63%) had a Ki-67 index of at least 30%. Although Ki-67 index with stratification below versus at or above 30% is emerging as a potential prognostic indicator in patients newly diagnosed with MCL, its role in predicting prognosis among the r/r population remains an open question. As such, no clinically meaningful information can be drawn at this time from the Ki-67 index groupings observed in ZUMA-2, and these data were not included in the product's prescribing information.

Overall, the data presented in this section illustrate that those enrolled in ZUMA-2 fairly represent the population with MCL that has relapsed after or is refractory to what are generally accepted as the most efficacious therapies currently available.

The ZUMA-2 protocol required confirmation of bone marrow aspirate/biopsy results at screening if these studies had not been performed fewer than four weeks prior to the patient signing informed consent. Individuals who received bridging therapy needed repeat bone marrow testing after completing bridging treatment and before beginning conditioning chemotherapy, if applicable. Twenty (33%) of the 60 IAS subjects met these bone marrow examination specifications. Table 10 summarizes details of the IAS's baseline bone marrow testing.

Table 10. Baseline bone marrow examinations among ZUMA-2's Inferential Analysis Set (IAS; n = 60).

	N (%)	Median days BMEP prior to conditioning	Range of days BMEP prior to conditioning
Received bridging therapy	21 (100%)	86	1 to 1620
BMEP per protocol	3 (14%)	1	1 to 1
BME not repeated between bridging and conditioning	18 (86%)	94	29 to 1620
Most recent prior BME result			
Positive	13 (62%)	86	29 to 1519
Indeterminate	1 (5%)	100	n/a
Negative	4 (19%)	166	33 to 1620
	N (%)	**Median days BMEP prior to consent**	**Range of days BMEP prior to consent**
Did not receive bridging therapy*	39 (100%)	190	-46** to 2823
BMEP per protocol	17 (44%)	-2	-46 to 29
No pre-treatment BME recorded	1 (3%)	n/a	n/a
BMEP > four weeks prior to consent	21 (54%)	1058	119 to 2823
Most recent prior BME result			
Positive	14 (36%)	1179	119 to 2823
Negative	7 (18%)	890	386 to 2258

BME = bone marrow examination, BMEP = bone marrow examination performed
**Median and range of days the bone marrow examination was performed prior to consent calculated with n = 38, because one subject of the 39 who did not receive bridging therapy did not have a pre-treatment bone marrow examination recorded.*
***Negative values indicate the bone marrow examination was performed after consent was signed.*

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Report Body, pages 30-34, and 5.3.5.2 Data Analysis Data, datasets ADLB and ADSL)

Clinical reviewer comments
One-third of subjects (20 of 60; 33%) met protocol-specified timing for baseline bone marrow examinations. The remaining two-thirds of subjects had their most recent pre-ZUMA-2 bone marrow assessments performed over a time frame encompassing more than seven and a half years (maximum interval 2823 days between bone marrow testing and signing of ZUMA-2 consent). Because of the wide variability affecting such a large proportion of subjects, no reliable conclusions regarding the group's baseline bone marrow disease status can be drawn. Additionally, uncertainty about true baseline bone marrow positivity versus negativity complicated disease response assessments for some subjects [see 6.1.11.1 Analyses of Primary Endpoint(s)].

6.1.10.1.3 Subject Disposition

Table 11. ZUMA-2 subject disposition.

	All, N (%)	Cohort 1, N (%)
Screened	122 (n/a)	n/a
Enrolled	91 (100%)	74 (100%)
Received bridging therapy	32 (35%)	25 (34%)
Began conditioning chemotherapy	84 (92%)	69 (93%)
Treated with KTE-X19	82 (90%)	68 (92%)
Reason for not proceeding with study treatment		
Any	9 (10%)	6 (8%)
Death	2 (2%)	1 (1%)
Manufacturing failure	4 (4%)	3 (4%)
Ineligibility	2 (2%)	1 (1%)
Consent withdrawal	1 (1%)	1 (1%)

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Report Body, Section 8.2 Disposition of Study Subjects, pages 56-59 of 997)

As shown in Table 11, 122 patients were screened for participation in ZUMA-2. Thirty-one of them (25%) did not meet the screening requirements, leaving 74 subjects to enroll in Cohort 1 and 17 subjects to enroll in Cohort 2. Subjects were considered enrolled at the time leukapheresis commenced. Among the 74 enrolled Cohort 1 subjects, 69 (93%) began conditioning chemotherapy and 68 (92%) were treated with KTE-X19. In Cohort 2, 15 (88%) of the 17 enrolled subjects began lymphodepletion, and 14 (82%) went on to receive KTE-X19 infusion. A summary of the resulting analysis populations is presented in Table 12.

Table 12. Key analysis population sets* in ZUMA-2.

	Cohort 1	Cohort 2	Overall
Inferential analysis set	60	n/a	60
Safety analysis set	68	14	82
Modified intent-to-treat analysis set	68	14	82
Full analysis set	74	17	91

**See 6.1.10.1 Populations Enrolled/Analyzed for analysis set definitions and brief descriptions of the analyses for which they were utilized.*

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Report Body and datasets)

A brief narrative for each subject enrolled in ZUMA-2 but not treated with KTE-X19 follows:

- Cohort 1 [n = 74 enrolled; six (8%) not treated with KTE-X19]
  - One subject died of progressive disease before KTE-X19 was delivered to the study site
  - Manufacturing failed for one subject who then died of progressive disease before leukapheresis was repeated for a second manufacturing attempt
  - One subject developed symptomatic deep vein thrombosis, therefore becoming ineligible for the study, after manufacturing failed and before leukapheresis was repeated for a second manufacturing attempt

  - One subject withdrew from the study after product manufacturing failed twice, from two sets of leukapheresis material
  - One subject withdrew from the study to receive an alternative treatment regimen; the study site returned this subject's KTE-X19 to the applicant
  - One subject began lymphodepleting chemotherapy before being found to have atrial fibrillation, making him/her ineligible for the study
- Cohort 2 [n = 17 enrolled; three (18%) of these not treated with KTE-X19]
  - One subject died of progressive disease before KTE-X19 was delivered to the study site
  - One subject experienced manufacturing failure and died of tumor lysis syndrome before leukapheresis was repeated for a second manufacturing attempt
  - One subject received conditioning chemotherapy but developed bacterial and viral infections which rendered him/her ineligible for the study

Clinical reviewer comments
The possibility of manufacturing failure must be considered during risk-benefit analysis of any autologous CAR T cell product. In ZUMA-2, 91 total subjects (74 in Cohort 1, 17 in Cohort 2) were leukapheresed, of which four (4%) were not treated due to manufacturing failure. This rate is on par with those of commercially available CAR T cell products.

Of note, manufacturing failed for one Cohort 1 subject who then died of progressive disease before leukapheresis was repeated for a second manufacturing attempt. To maintain clarity, this subject was counted only once—as a manufacturing failure—in Table 11 and in the prescribing information's discussion of why enrolled subjects were not treated with KTE-X19.

Table 13 describes the KTE-X19 manufacturing times observed during the study.

Table 13. KTE-X19 manufacturing times during ZUMA-2.

	IAS	Cohort 1	Cohort 2	All
Number of subjects who had KTE-X19 delivered to their clinical site	60	70	15	85
Days from leukapheresis to KTE-X19 delivery				
Median	15	16	14	15
Minimum	11	11	12	11
Maximum	28	128	16	128
	IAS	**Cohort 1**	**Cohort 2**	**All**
Number of subjects who had KTE-X19 infused	60	68	14	82
Days from leukapheresis to KTE-X19 infusion				
Median	27	27	26	27
Minimum	19	19	15	15
Maximum	63	134	34	134

IAS = inferential analysis set

(Source: FDA clinical reviewer's compilation from BLA 125703/0.0, 5.3.5.2 Data Analysis Data, datasets ADDA and ADEX)

Clinical reviewer comments

Product manufacturing times are particularly relevant for patients with r/r disease, which is often aggressive and rapidly progressive. In this context, prolonged manufacturing times increase risk of morbidity and mortality. During ZUMA-2, the median time from leukapheresis to KTE-X19 delivery was 15 days, and from leukapheresis to KTE-X19 infusion was 27 days. These intervals are consistent with those of currently marketed CAR T cell products. The low death rate during manufacturing (see Table 11 in 6.1.10.1 Populations Enrolled/Analyzed and discussion above) supports the acceptability of the duration of KTE-X19's current manufacturing process.

One non-IAS Cohort 1 subject recorded a 128-day interval between leukapheresis and KTE-X19 delivery, with 134 days between leukapheresis and KTE-X19 infusion. This subject experienced a complete response to bridging therapy after leukapheresis, so his/her manufactured product was stored. When his/her disease progressed approximately three months later, the original product was shipped and infused. Considering the Cohort 1 population without the outlier results in a median time between leukapheresis and product delivery or infusion of 16 or 27 days, respectively; considering the entire ZUMA-2 population without the outlier gives a median of 15 or 27 days, respectively, elapsed between leukapheresis and product delivery or infusion. These intervals are nearly identical to those calculated when including the outlier subject, indicating that this individual's unique situation did not unduly influence the observed overall timeframes and supporting the robustness of the data.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary objective of ZUMA-2 [6.1.1 Objectives (Primary, Secondary, etc)] was to evaluate the efficacy of KTE-X19 in subjects with r/r MCL by measuring the primary endpoint (6.1.8 Endpoints and Criteria for Study Success) of ORR as assessed centrally using the 2014 Lugano Classification.

Baseline disease and disease response were assessed at each timepoint both by the site investigator and by an Independent Radiology Review Committee (IRRC; central). Two central radiologists read each subject's images timepoint by timepoint. If the central radiologists' assessments differed, a third radiologist acted as an adjudicator. After adjudication (if applicable), a central clinician reviewed the imaging data in conjunction with clinical data to provide a final central disease status assessment. As discussed in the clinical reviewer comment in 6.1.8 Endpoints and Criteria for Study Success, investigators applied IWG 2007 criteria, while central assessors followed the 2014 Lugano Classification.

Four subjects (7%) in the inferential analysis set (IAS; n = 60) were reclassified by FDA from responders [one complete response (CR), three partial responses (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.

Two additional subjects (3%) in the IAS (n = 60) were reclassified by FDA from best objective response (BOR) of CR to BOR of PR. One subject had established a PR at the first two follow-up timepoints, based on CR by imaging without the confirmation of a negative bone marrow exam (required because the subject's baseline bone marrow status was unknown). At the third disease response assessment timepoint, central evaluators assessed CR while the site investigator assessed PD. Further investigation revealed that both the investigator and the central adjudicating radiologist identified a new area of hypermetabolic rectal wall thickening on the third follow-up timepoint's positron-emission tomography (PET) scan. The lesion enlarged on subsequent imaging, confirming PD, followed by initiation of new anti-lymphoma treatment. ZUMA-2's imaging charter defines the date selection criterion for PD as "The earliest date where there is evidence of PD"; thus, the third follow-up timepoint (Month 6) was correctly assessed as PD, not CR.

In a similar scenario, the second subject reclassified from BOR of CR to BOR of PR established PR at the first follow-up timepoint based on CR by imaging without the confirmation of a negative bone marrow exam (required because the subject's baseline bone marrow status was unknown). CR by imaging persisted at the second follow-up timepoint. Negative bone marrow testing was subsequently performed, and an overall assessment of CR was retrospectively assigned to the second follow-up timepoint. However, ZUMA-2's imaging charter instructed central clinicians to base their assessments on the relevant timepoint's imaging as well as clinical information dated within two weeks before or after the imaging dates for the relevant timepoint, and this subject's negative bone marrow was performed outside the specified time frame. As

such, the bone marrow data could not be applied to the second follow-up timepoint. The reported CR was corrected to PR. At the third follow-up timepoint, CR was again demonstrated by imaging, but less than two weeks later—within the charter-specified window of application to the overall timepoint assessment—the subject's bone marrow biopsy revealed lymphoma involvement and thus PD.

Results of the primary endpoint analysis are shown in Table 14.

Table 14. ZUMA-2 objective response rate (ORR); central analysis per 2014 Lugano Classification (IAS, n = 60).

	FDA Analysis % (n), [95% CI]	**Applicant Analysis** % (n), [95% CI]
ORR	87% (52), [75.4 – 94.1]	93% (56), [83.8 – 98.2]

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)

Clinical reviewer comments

As displayed in Table 14, treatment with KTE-X19 in ZUMA-2 resulted in a high ORR that was not meaningfully changed by FDA's re-adjudications. This ORR may be placed in context by considering the ORRs observed in the pivotal studies of each of the agents currently approved to treat relapsed/refractory MCL [Table 1, 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)], which ranged from 26% to 84%. The outcomes cannot be directly compared because the studies enrolled different patient populations, were conducted under different conditions, and assessed disease responses using different criteria. Even so, the historical ORRs provide a general framework within which to interpret the results of ZUMA-2 and demonstrate that treatment with KTE-X19 led to an ORR comparable or superior to those achieved with the approved products.

ORR is a critical component of the risk-benefit analysis performed to recommend approving or not approving a product's licensure. Here, the ORR is favorable. But, high response rates are seen with many therapies used to treat MCL, only to be followed by high rates of relapse. As such, duration of response is particularly important in the evaluation of MCL-directed treatments and is discussed for KTE-X19 in 6.1.11.2 Analyses of Secondary Endpoints. Safety is always paramount and is assessed in 6.1.12 Safety Analyses.

6.1.11.2 Analyses of Secondary Endpoints

ZUMA-2 had several secondary endpoints (6.1.8 Endpoints and Criteria for Study Success): best overall response (BOR) by central evaluation, objective response rate (ORR) and BOR by investigator evaluation, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Data for each are presented here in Tables 15 through 18 and Figure 1, with definitions detailed in 6.1.9 Statistical Considerations & Statistical Analysis Plan.

Table 15. Best objective responses in ZUMA-2; central analysis per 2014 Lugano Classification (IAS, n = 60).

	FDA Results n (%) [95% CI]	**Applicant Results** n (%) [95% CI]
CR	37 (62%) [48.2 – 73.9]	40 (67%) [53.3 – 78.3]
PR	15 (25%) [14.7 – 37.9]	16 (27%) [16.1 – 39.7]
SD	2 (3%) [0.4 – 11.5]	2 (3%) [0.4 – 11.5]
PD	3 (5%) [1.0 – 14.0]	2 (3%) [0.4 – 11.5]
NR	3 (5%) [1.0 – 14.0]	n/a

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)

Clinical reviewer comment
The majority of subjects treated with KTE-X19 responded with CRs, while an additional quarter experienced PRs. These are significantly positive results considering the r/r population enrolled on ZUMA-2.

Table 16. Objective response rate and best overall responses in ZUMA-2; investigator analysis per 2007 IWG Criteria (IAS, n = 60).

	Results, n (%) [95% CI]
ORR	53 (88%) [77.4 - 95.2]
CR	42 (70%) [56.8 - 81.2]
PR	11 (18%) [9.5 – 30.4]
SD	5 (8%) [2.8 – 18.4]
PD	2 (3%) [0.4 – 11.5]

CI = confidence interval, CR = complete response, IAS = inferential analysis set, ORR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease

(Source: Adapted from BLA 125703/0.0, 5.3.5.2 Report Body Table 15, page 84 of 997)

Clinical reviewer comment
The responses observed by site investigators using the 2007 IWG Criteria (Table 16) were similar to those observed centrally using the 2014 Lugano Classification (Table 15 in 6.1.11.2 Analyses of Secondary Endpoints). This speaks to the robustness of the study results, supporting the favorable efficacy of KTE-X19.

During the BLA review, FDA adjudicated the applicant's reported time to best response for seven (12%) subjects and duration of response (DOR) for three (5%) subjects among the 60 subjects of the IAS. These adjustments were made primarily by application of ZUMA-2's imaging charter's date selection criteria (BLA 125703/0.0, 5.3.5.2, Imaging

Review Charter, Table 13, page 83 of 88) and timepoint response assessment guidance (BLA 125703/0.0, 5.3.5.2, Imaging Review Charter, Table 9, page 68 of 88). The resulting time to response data are shown in Table 17, while duration of response data are found in Table 18. Of the 60 subjects in the IAS, 49 (82%) responded at their first post-treatment follow-up timepoint (Week 4), while an additional three (5%) responded at their second post-treatment follow-up timepoint (Month 3). 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 duration of response. One subject had a DOR of 0 days. This subject demonstrated PR at his/her first post-treatment disease response assessment, then began new anti-MCL therapy before his/her second follow-up timepoint. Per ZUMA-2's statistical plan, when a subject began new anti-MCL therapy, his/her date of disease progression was censored to his/her most recent disease response evaluation. As a result, this subject's date of first response and censored date of progression fell on the same day, giving a DOR of 0 days.

Table 17. Time to response results in ZUMA-2; FDA analysis (IAS, n = 60).

	Days to First Response
Mean	32
Standard deviation	15
Median	28
Minimum	24
Maximum	92

(Source: FDA clinical reviewer)

Table 18. 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%

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)

Clinical reviewer comments

FDA adjudicated the applicant's submitted response timing data for several subjects in accordance with the study's imaging charter. The applicant's reported centrally-evaluated median DOR for the IAS was not reached, with a 95% confidence interval lower bound of 8.6 months and upper bound not estimable given a censoring rate of 70% (39 of 56 responding subjects; BLA 125703/0.0, 5.3.5.2 Report Body Table 19, page 102 of 997). The similarity of the applicant's reported results to FDA's calculations summarized in Table 18 demonstrate the insignificant nature of FDA's response timing corrections and support the robustness of the submitted data.

Three subjects in the IAS experienced their first response at their Month 3 post-KTE-X19 infusion follow-up assessment. Of these, one was a CR and two were PRs that subsequently deepened to CRs. This demonstrates that although most responses occur acutely, a minority, including CRs, may develop over time.

As mentioned above, the median DOR in ZUMA-2 could not be estimated because of the high proportion of censoring. The same is true for the median DOR within the CR subgroup, where 84% were censored for progression. Despite these limitations, the data show that those whose disease responded completely (CR) to KTE-X19 experienced more persistent responses than those whose best disease response was PR.

The available data allow only superficial comparison to other products. As shown in Table 1 in 2.2 Currently Available, Pharmacologically Unrelated

Treatment(s)/Intervention(s) for the Proposed Indication(s), the median DOR observed among agents with full or accelerated approval for treatment of r/r MCL ranges from 9.3 months for the oldest drug, bortezomib, to around 19 months for the most recently approved therapy, zanubrutinib. Acalabrutinib's median DOR was not estimable at the time of approval. ZUMA-2's available data estimate a minimum bound of the 95% confidence interval around the median DOR of approximately one year, but cannot speak to a median point estimate.

Median progression-free and overall survival could not be estimated because fewer than half the subjects died or experienced disease progression prior to censoring. These data are depicted in Figure 1.

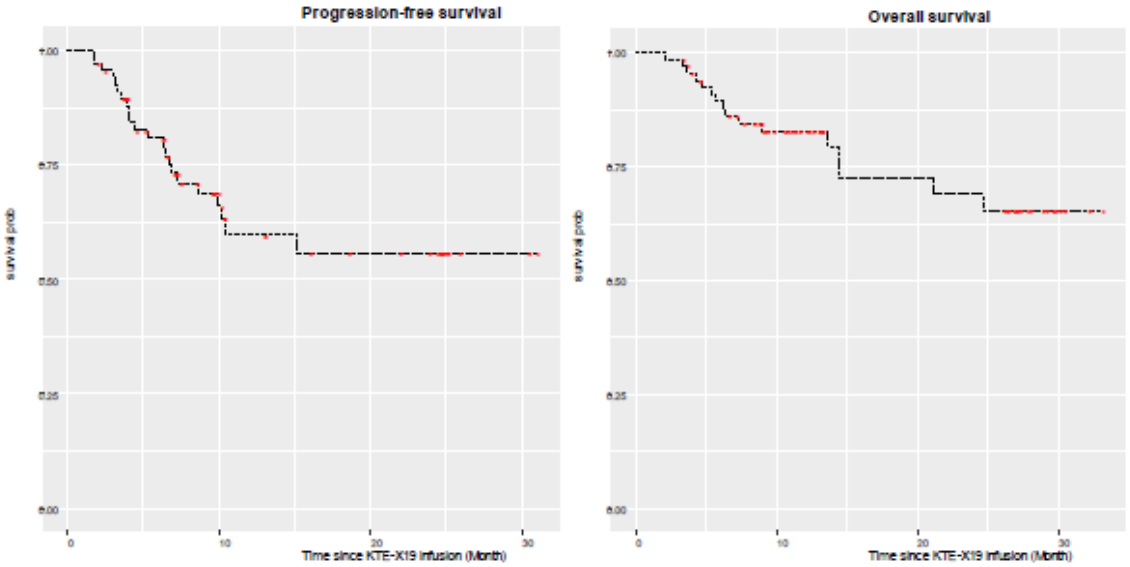

Figure 1. Progression-free survival and overall survival in ZUMA-2 (SAS/mITTAS, n = 68).
(Source: FDA statistical reviewer)

Clinical reviewer comments
Due to the lack of a comparator control group, interpretation of survival data from single arm studies is limited.

Please refer to the statistical review memorandum for further analyses.

6.1.11.3 Subpopulation Analyses

Subgroup analyses of ORR within the IAS according to several key baseline demographic and disease characteristics are presented in a forest plot in Figure 2.

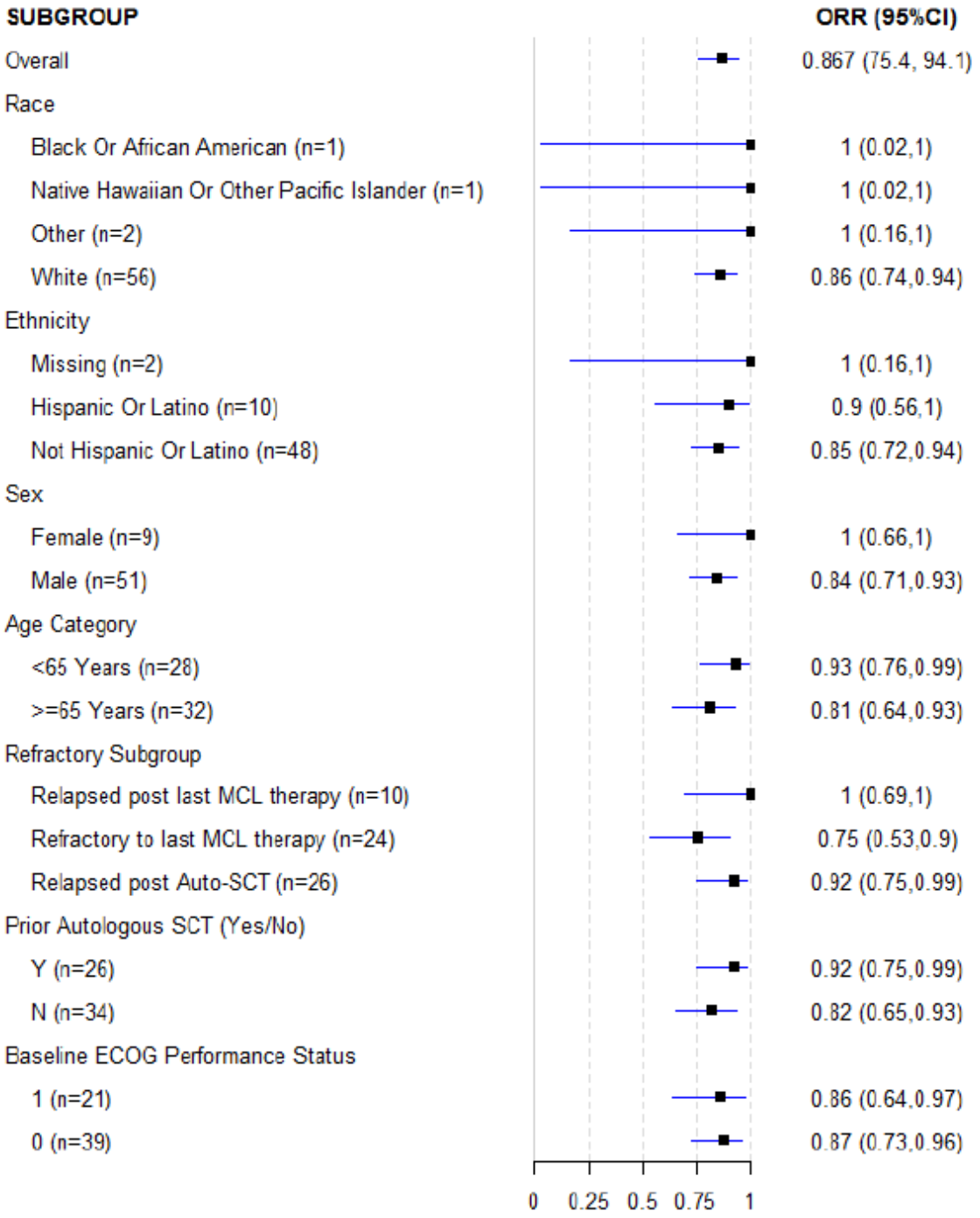

Figure 2. Forest plot subgroup analysis of objective response rate (ORR) per central assessment (IAS, n = 60).
(Source: FDA statistical reviewer)

Clinical reviewer comment
The populations within some subgroup categories were very small, limiting data interpretation. However, in general, ORR appears similar across race, ethnicity, sex, age category, refractory subgroup, exposure to prior autoHSCT, and performance status. No

subgroup analysis by country was done because only one IAS subject was treated outside the United States.

Further details of response by age and by sex are provided in Tables 19 and 20, respectively.

Table 19. ZUMA-2 response rates by age category (IAS, n = 60).

	Age < 65 Years	**Age >/= 65 Years**
Total N	28	32
PR, N (%) [95% CI]	9 (32%) [15.9 – 52.4]	6 (19%) [7.2 – 36.4]
CR, N (%) [95% CI]	17 (61%) [40.6 – 78.5]	20 (63%) [43.7 – 78.9]
ORR, N (%) [95% CI]	26 (93%) [76.5 – 99.1]	26 (81%) [63.6 – 92.8]

CI = confidence interval, CR = complete response, ORR = objective response rate, PR = partial response

(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, and multiple information requests)

Table 20. ZUMA-2 response rates by sex (IAS, n = 60).

	Females	**Males**
Total N	9	51
PR, N (%) [95% CI]	4 (44%) [13.7 – 78.8]	11 (22%) [11.3 – 35.3]
CR, N (%) [95% CI]	5 (56%) [21.2 – 86.3]	32 (63%) [48.1 – 75.9]
ORR, N (%) [95% CI]	9 (100%) [66.4 – 100]	43 (84%) [71.4 – 93.0]

CI = confidence interval, CR = complete response, ORR = objective response rate, PR = partial response

(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, and multiple information requests)

Tables 21, 22, and 23 stratify response rates according to subjects' number of prior lines of therapy, response to last BTK inhibitor, and receipt of bridging therapy between completing leukapheresis and beginning conditioning chemotherapy, respectively.

Table 21. ZUMA-2 response rates by number of prior lines of therapy (IAS, n = 60).

	Two Prior Lines of Therapy	More Than Two Prior Lines of Therapy
Total N	12	48
PR, N (%) [95% CI]	4 (33%) [9.9 – 65.1]	9 (19%) [9.0 – 32.6]
CR, N (%) [95% CI]	7 (60%) [27.7 – 84.8]	32 (67%) [51.6 – 79.6]
ORR, N (%) [95% CI]	11 (92%) [61.5 – 99.8]	41 (85%) [72.2 – 93.9]

CI = confidence interval, CR = complete response, ORR = objective response rate, PR = partial response

(Source: FDA statistical and clinical reviewers)

Table 22. ZUMA-2 response rates by response to last BTK inhibitor (IAS, n = 60).

	Refractory	Relapsed or Intolerant	< 6 Months From Last BTKi to KTE-X19 Infusion	>/= 6 Months From Last BTKi to KTE-X19 Infusion
Total N	42	18	11	7
PR, N (%) [95% CI]	12 (29%) [15.7 – 44.6]	3 (17%) [3.6 – 41.4]	1 (9%) [0.2 – 41.3]	2 (29%) [3.7 – 71.0]
CR, N (%) [95% CI]	23 (55%) [38.7 – 70.2]	14 (78%) [52.4 – 93.6]	10 (91%) [58.7 – 99.8]	4 (57%) [18.4 – 90.1]
ORR, N (%) [95% CI]	35 (83%) [68.6 – 93.0]	17 (94%) [72.7 – 99.9]	11 (100%) [71.5 – 100]	6 (86%) [42.1 – 99.6]

CI = confidence interval, CR = complete response, ORR = objective response rate, PR = partial response

(Source: FDA statistical and clinical reviewers)

Table 23. ZUMA-2 response rates by receipt of bridging therapy (IAS, n = 60).

	Received Bridging Therapy	Did Not Receive Bridging Therapy
Total N	21	39
PR, N (%) [95% CI]	10 (48%) [25.7 – 70.2]	5 (13%) [4.3 – 27.4]
CR, N (%) [95% CI]	6 (29%) [11.3 – 52.2]	31 (79%) [63.5 – 90.7]
ORR, N (%) [95% CI]	16 (76%) [52.8 – 91.8]	36 (92%) [79.1 – 98.4]

CI = confidence interval, CR = complete response, ORR = objective response rate, PR = partial response

(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, and multiple information requests)

Clinical reviewer comments

No significant difference in response rates was detected based upon two versus more than two prior lines of therapy. Any effect number of prior lines of therapy could have on efficacy outcomes may have been minimized because all subjects had previously been treated with anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a BTK inhibitor, so the study population was controlled for key

prior exposures. The exceptions to these prior exposures were one subject who had not received either an anthracycline or bendamustine, and a second subject who had been given only a single dose of ibrutinib.

Response rates remained consistent between subgroups refractory to BTK inhibitors and those relapsed after or intolerant to BTK inhibitor therapy.

Although ORR was similar regardless of administration of bridging therapy, it is interesting to note that, among those who were given bridging therapy, PRs after KTE-X19 were more common than CRs. This is a reversal of the relative proportions seen in the overall study population and in the other subgroups analyzed. One potential explanation is that subjects whom investigators elected to treat with bridging therapy while awaiting KTE-X19 manufacturing may have had more aggressive disease or poorer health at baseline than subjects whom investigators chose not to treat with bridging therapy. Regardless of etiology, this finding does not change the overall efficacy conclusions drawn from ZUMA-2 data.

6.1.11.5 Exploratory and Post Hoc Analyses

Patient-reported outcomes

One of ZUMA-2's secondary objectives was to assess the change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6 after KTE-X19 infusion [6.1.1 Objectives (Primary, Secondary, etc)]. The instrument domains are mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each domain allows a spectrum of five responses from none or no problems to extreme or unable to engage in the activity. In addition to these, scores from a visual analog scale (VAS) ranging from zero to 100 are included at each timepoint. EQ-5D surveys were administered at baseline and at Week 4, Month 3, and Month 6 after KTE-X19 infusions. These data are summarized in Table 24.

Table 24. Summary of European Quality of Life—5 Dimensions (EQ-5D) data collected during ZUMA-2 (Cohort 1 SAS/mITTAS, n = 68).

EQ-5D DIMENSION	Screening	Week 4	Month 3	Month 6
Mobility				
n	62	51	54	40
No problems walking, n (%)	53 (85)	25 (49)	37 (69)	30 (75)
Slight problems walking, n (%)	7 (11)	17 (33)	10 (19)	5 (13)
Moderate problems walking, n (%)	2 (3)	3 (6)	4 (7)	3 (8)
Severe problems walking, n (%)	0 (0)	4 (8)	2 (4)	2 (5)
Unable to walk, n (%)	0 (0)	2 (4)	1 (2)	0 (0)
Subject with deterioration from screening	n/a	21 (41)	13 (24)	8 (20)
Self-Care				
n	62	52	54	40
No problems washing or dressing, n (%)	59 (95)	35 (67)	45 (83)	37 (93)
Slight problems washing or dressing, n (%)	2 (3)	9 (17)	6 (11)	1 (3)
Moderate problems washing or dressing, n (%)	1 (2)	2 (4)	2 (4)	0 (0)
Severe problems washing or dressing, n (%)	0 (0)	4 (8)	1 (2)	2 (5)
Unable to wash or dress, n (%)	0 (0)	2 (4)	0 (0)	0 (0)
Subject with deterioration from screening	n/a	16 (31)	9 (17)	3 (8)
Usual Activity				
n	65	51	55	41
No problems doing usual activities, n (%)	53 (82)	22 (43)	38 (69)	30 (73)
Slight problems doing usual activities, n (%)	9 (14)	12 (24)	9 (16)	7 (17)
Moderate problems doing usual activities, n (%)	3 (5)	11 (22)	4 (7)	3 (7)
Severe problems doing usual activities, n (%)	0 (0)	3 (6)	2 (4)	0 (0)
Unable to do usual activities, n (%)	0 (0)	3 (6)	2 (4)	1 (2)
Subject with deterioration from screening	n/a	25 (49)	13 (24)	8 (20)
Pain / Discomfort				
n	65	54	55	42
No pain or discomfort, n (%)	43 (66)	34 (63)	33 (60)	28 (67)
Slight pain or discomfort, n (%)	14 (22)	10 (19)	9 (16)	9 (21)
Moderate pain or discomfort, n (%)	6 (9)	10 (19)	10 (18)	4 (10)
Severe pain or discomfort, n (%)	2 (3)	0 (0)	2 (4)	1 (2)
Extreme pain or discomfort, n (%)	0 (0)	0 (0)	1 (2)	0 (0)
Subject with deterioration from screening	n/a	9 (17)	13 (24)	5 (12)
Anxiety / Depression				
n	65	54	55	42
Not anxious or depressed, n (%)	49 (75)	36 (67)	38 (69)	26 (62)
Slight anxious or depressed, n (%)	13 (20)	14 (26)	12 (22)	11 (26)
Moderate anxious or depressed, n (%)	3 (5)	3 (6)	5 (9)	5 (12)
Severe anxious or depressed, n (%)	0 (0)	1 (2)	0 (0)	0 (0)
Extreme anxious or depressed, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Subject with deterioration from screening	n/a	11 (20)	12 (22)	10 (24)

Data cutoff date = 24JUL2019
Abbreviations: VAS, Visual Analogue Scale.
Missing assessment is not included in the summary.
Percentages are based on the number of subjects with a non-missing assessment of an EQ dimension at each visit unless specified otherwise.
Deterioration of an EQ dimension means the dimension worsened by at least 1 level from screening.
The EQ VAS ranges from 0 to 100 with a higher score indicating a better health state.

Data Source: ADSL, ADQS Program Name: t_eq5d_vas Output Generated: 20191008T16:12

EQ-5D DIMENSION	Screening	Week 4	Month 3	Month 6
EQ VAS				
n	65	52	55	42
Mean (StD)	82.0 (15.4)	74.5 (15.6)	80.1 (15.6)	84.8 (17.5)
Median (Q1, Q3)	85.0 (75.0, 95.0)	78.0 (60.0, 89.0)	83.0 (70.0, 92.0)	90.0 (80.0, 95.0)
Min, max	45, 100	38, 100	40, 100	20, 100
VAS reduced by ≥ 10 from screening	n/a	26 (50)	16 (29)	5 (12)

Data cutoff date = 24JUL2019
Abbreviations: VAS, Visual Analogue Scale.
Missing assessment is not included in the summary.
Percentages are based on the number of subjects with a non-missing assessment of an EQ dimension at each visit unless specified otherwise.
Deterioration of an EQ dimension means the dimension worsened by at least 1 level from screening.
The EQ VAS ranges from 0 to 100 with a higher score indicating a better health state.

Data Source: ADSL, ADQS Program Name: t_eq5d_vas Output Generated: 20191008T16:12

(Source: Original BLA 125703/0.0, 5.3.5.2 Report Body Table 14.2.16.1a, page 390-391 of 997)

Clinical reviewer comments

In the functional categories of mobility, self-care, and usual activity, and echoed in median VAS scores, the general trend was toward worsening from baseline to Week 4, followed by gradual improvement at Months 3 and 6. Results in the pain/discomfort and anxiety/depression domains remained stable throughout the study. Several caveats must be kept in mind when interpreting the meaning behind these observations. First, ZUMA-2 was a single arm study. There is no control or alternative treatment group with which to compare quality of life rating patterns. Second, subjects may be biased toward reporting worse scores before and better scores after administration of study treatment. Third, there was a 35% (23 of 65 subjects, or 22 of 62 subjects, depending on the measured dimension) drop-out rate from baseline to Month 6. Many factors may have contributed to this attrition, including the possibility that subjects experiencing worse quality of life were more likely to drop out or die, spuriously making the group's scores appear to improve over time.

Product Dose Administered

The ZUMA-2 protocol specified a target dose for Cohort 1 subjects of 2 x 10^6 CAR-positive viable T cells/kg, to be administered as a single intravenous infusion. A minimum dose of (b) (4) CAR-positive viable T cells/kg was allowed, while subjects weighing 100 kg or more were to receive a maximum flat dose of 2 x 10^8 CAR-positive viable T cells. Among the 60 IAS subjects, 54 (90%) were infused with the target 2 x 10^6 CAR-positive viable T cells/kg. The six (10%) remaining subjects were given smaller doses, which are detailed in Table 25 along with each subject's best objective disease response.

Table 25. Sub-target KTE-X19 doses administered during ZUMA-2 and corresponding best objective responses (IAS, n = 60).

Subject ID	Infused Dose (x 10^6 CAR-positive viable T cells/kg)	Best Objective Response
(b) (6)	1.0	CR
	1.6	PR
	1.8	CR
	1.8	PR
	1.9	CR
	1.9	PR

CR = compete response, PR = partial response

(Source: FDA clinical reviewer's compilation from several BLA 125703/0.0, 5.3.5.2 Data Analysis Data datasets)

Summary disease responses for those administered 2 x 10^6 CAR-positive viable T cells/kg or fewer than 2 x 10^6 CAR-positive viable T cells/kg are shown in Tables 26 and 27, respectively.

Table 26. Objective response rate and best overall responses among subjects infused with 2 x 10^6 KTE-X19 cells/kg (IAS, n = 60).

	N	% of 54	95% CI
Received 2e6 KTE-X19/kg	54	100%	n/a
ORR	46	85%	72.9 - 93.4
CR	34	63%	48.7 - 75.7
PR	12	22%	12.0 – 35.6

CI = confidence interval, CR = complete response, n/a = not applicable, ORR = objective response rate, PR = partial response

(Source: FDA clinical reviewer's calculations)

Table 27. Objective response rate and best overall responses among subjects infused with fewer than 2 x 10^6 KTE-X19 cells/kg (IAS, n = 60).

	N	% of 6	95% CI
Received fewer than 2e6 KTE-X19/kg	6	100%	n/a
ORR	6	100%	54.1 – 100
CR	3	50%	11.8 – 88.2
PR	3	50%	11.8 – 88.2

CI = confidence interval, CR = complete response, n/a = not applicable, ORR = objective response rate, PR = partial response

(Source: FDA clinical reviewer's calculations)

Clinical reviewer comments

Each of the 60 subjects included in the IAS received an acceptable dose of KTE-X19 according to the protocol's requirements. All subjects who received less than the target dose of KTE-X19 responded to study treatment. Best responses were evenly split between PRs and CRs, as compared to a preponderance of CRs in those given the

target 2 x 10^6 CAR-positive viable T cells/kg. However, with only six individuals, the population of IAS subjects infused with less than 2 x 10^6 CAR-positive viable T cells/kg is too small to support sound dose-response correlation or efficacy conclusions. To reflect that the available data only support efficacy of KTE-X19 when administered at 2 x 10^6 CAR-positive viable T cells/kg, the prescribing information's proposed language of "target dose" of 2 x 10^6 CAR-positive viable T cells/kg was revised to "dose" of 2 x 10^6 CAR-positive viable T cells/kg.

Of the eight subjects treated in Cohort 1 but not included in the IAS due to lack of sufficient follow-up, seven received 2 x 10^6 CAR-positive viable T cells/kg. The remaining subject received 0.6 x 10^6 CAR-positive viable T cells/kg. For this subject, the first manufacturing attempt produced 0.6 x 10^6 CAR-positive viable T cells/kg. Although below the protocol-specified range, the treating investigator believed it was in the subject's best interest to administer the available dose, rather than repeat leukapheresis and manufacturing, because of the subject's disease progression subsequent to the first round of leukapheresis. A waiver to proceed with treatment at the lower dose was requested from, and granted by, FDA. The 0.6 x 10^6 CAR-positive viable T cells/kg dose was administered, and CR was observed at the subject's Week 4 disease response assessment. CR persisted at his/her most recent disease response assessment 49 days later. This subject's underdosing was not considered an important protocol deviation by the applicant and does not change ZUMA-2's efficacy conclusions.

The applicant's proposed KTE-X19 lot release specification criteria for dose were (b) (4) *CAR-positive viable T cells/kg to* (b) (4) *CAR-positive viable T cells/kg, with a maximum allowable flat dose of 2.0 x 10^8 CAR-positive viable T cells for patients weighing 100 kg or more. Considering all 68 treated subjects in Cohort 1, 61 (90%) received the target dose of 2 x 10^6 CAR-positive viable T cells/kg. The subpopulation of seven (10%) subjects who received less than the target dose is too small to adequately evaluate product efficacy, and no subject was administered a dose higher than the target. As such, only the applicant's original target dose, and not their proposed dose range, can be verified based on ZUMA-2 data. To reflect these conclusions, the applicant revised their KTE-X19 lot release specification criteria for dose at FDA's request to 2 x 10^6 CAR-positive viable T cells/kg, with a maximum allowable flat dose of 2 x 10^8 CAR-positive viable T cells for patients weighing 100 kg or more.*

6.1.12 Safety Analyses

6.1.12.1 Methods

The key materials used for the safety review included:

- The BLA application electronic submission
- Applicant submissions in response to the review team's information requests
- Proposed labeling for KTE-X19
- Published literature
- Prior regulatory history

The clinical review of safety was primarily based upon analysis of ZUMA-2. The KTE-X19-102 datasets were used for the safety analysis. Analyses by the clinical reviewer for safety were performed largely using JMP 13. All narratives and relevant case report forms (CRFs) were reviewed for all serious adverse events (AEs) and deaths that

occurred in the primary safety population within 30 days of receiving KTE-X19. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0, and AE severity was graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) severity was graded as a syndrome according to a modification of the Lee criteria grading system. Some AEs are presented throughout this review as grouped terms as defined by the review team. The complete list of FDA's grouped terms is presented in Appendix A. Unless otherwise specified, all analyses and tables were generated by the FDA clinical reviewer.

The safety analysis set included all subjects treated with any dose of KTE-X19. All AEs were collected from the start of leukapheresis until 90 days after KTE-X19 infusion. Serious adverse event (SAE) were defined as any AEs that met at least one of the following criteria: fatal, life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, resulted in congenital anomaly or birth defect, or resulted in any other medically important serious event. SAEs were collected from the time of screening. Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring after the start of KTE-X19 administration. Adverse drug reactions (ADRs) were defined as any AEs occurring after the start of KTE-X19 infusion, regardless of perceived relationship with the investigational product. From Month 3 to Month 24 or disease progression, whichever occurred first, only the following AEs/SAEs were collected: hematologic events, neurologic events, infections, autoimmune disorders, and secondary malignancies.

Clinical reviewer comment
The applicant's definition of adverse drug reactions aligns with the reviewer's; however, the adverse reactions are reported by the applicant's preferred term, which may underestimate some AEs. To minimize underestimation of AE events, FDA grouped preferred terms that represent the same disease process. The reviewer utilized a grouping strategy for comprehensive analyses of AEs that is consistent with the grouping practices for review of similar agents within this class of therapies. Please refer to Appendix A for the full list of FDA's grouped terms.

Safety analysis was conducted on the complete dataset provided by the applicant for study ZUMA-2, including all subjects who were enrolled (i.e., leukapheresed) in both Cohort 1 and Cohort 2, with a data cutoff date of 24 July 2019. In addition, safety analysis was also performed on the applicant's 120-day safety update with a data cutoff date of 31 December 2019.

The demographic information and subject disposition for the subjects evaluated for safety are summarized in the tables below. The median duration of follow-up for safety in Cohort 1 was 10.3 months (range 1.2 to 32.3 months). The median duration of follow-up in Cohort 2 was 15.0 months (range 0.6 to 18.0 months).

Table 28. Demographics of the safety population in ZUMA-2.

Characteristic	Statistics	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
Age group (years)	< 65	29 (43%)	11 (79%)	40 (49%)
	>/= 65	39 (57%)	3 (21%)	42 (51%)
	>/= 75	2 (3%)	0 (0%)	2 (2%)
	Mean (SD)	63.1 (7.9)	61.8 (5.4)	62.9 (7.5)
	Median (range)	65 (38 – 79)	61.5 (52 – 73)	65 (38 – 79)
Sex	Male	57 (84%)	11 (79%)	68 (83%)
	Female	11 (16%)	3 (21%)	14 (17%)
Race	White	62 (91%)	13 (93%)	75 (91%)
	Other	4 (6%)	1 (7%)	5 (6%)
	Black or African American	1 (1%)	0 (0%)	1 (1%)
	Native Hawaiian or Other Pacific Islander	1 (1%)	0 (0%)	1 (1%)
Ethnicity	Not Hispanic or Latino	55 (81%)	12 (86%)	67 (82%)
	Hispanic or Latino	11 (16%)	2 (14%)	13 (16%)
	Unknown	2 (3%)	0 (0%)	2 (3%)
Country	United States	62 (91%)	14 (100%)	76 (93%)
	France	3 (4%)	0 (0%)	3 (4%)
	Netherlands	2 (3%)	0 (0%)	2 (2%)
	Germany	1 (1%)	0 (0%)	1 (1%)
ECOG performance status	0	44 (65%)	7 (50%)	51 (62%)
	1	24 (35%)	7 (50%)	31 (38%)

ECOG = Eastern Cooperative Oncology Group, SD = standard deviation

(Source: FDA analysis of adsl.xpt)

Table 29. ZUMA-2 subject disposition.

Characteristic	Statistics	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
End of study status	Death	16 (24%)	4 (29%)	20 (24%)
Reason for discontinuation from study	Death	16 (24%)	4 (29%)	20 (24%)
End of treatment status	Completed	68 (100%)	14 (100%)	82 (100%)
Reason for discontinuation of treatment	Completed	68 (100%)	14 (100%)	82 (100%)
End of Month 3 status	Completed follow-up	59 (87%)	12 (86%)	71 (87%)
	Disease progression	4 (6%)	1 (7%)	5 (6%)
	Death	1 (1%)	1 (7%)	2 (2%)
	Withdrawal	1 (1%)	0 (0%)	1 (1%)

Data cutoff 24 July 2019

(Source: FDA analysis of adsl.xpt)

The number of prior chemotherapy regimen subjects received prior enrollment in the ZUMA-2 study is listed in Table 3. All subjects received prior anti-CD20 therapies and BTK inhibitor (ibrutinib or acalabrutinib) therapies. Sixty subjects (73%) received anthracyclines. Thirty-six subjects (43%) received prior autoSCT. Thirty-four subjects (41%) had refractory disease.

Table 30. Number of prior lines of therapy received by ZUMA-2 subjects.

Characteristic	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
Mean (SD)	3.3 (1.0)	3.3	3.3 (1.0)
Median	3	3	3
Min, max	1, 5	2, 5	1, 5
1	1 (1%)	0 (0%)	1 (1%)
2	12 (15%)	2 (14%)	14 (17%)
3	30 (37%)	8 (57%)	38 (46%)
4	14 (17%)	2 (14%)	16 (19%)
5	11 (13%)	2 (14%)	13 (16%)

Max = maximum, min = minimum, SD = standard deviation
Data cutoff 24 July 2019

(Source: FDA analysis of adbe.xpt)

Clinical reviewer comment
Subjects enrolled in ZUMA-2 were heavily pretreated patients who had received all the generally accepted standard MCL treatment regimens. The sponsor had strict eligibility enrollment criteria (ECOG performance status, organ function, and prior therapies). The safety population reflects subjects without significant organ dysfunction, and therefore safety findings from this population may be different than a population with significant comorbidities.

6.1.12.2 Overview of Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) were evaluated during clinic visits, hospitalizations, and follow-up visits per protocol-defined guidelines. Safety data are available for a total of 82 subjects who received KTE-X19 before the data cutoff of 24 July 2019. Adverse events and deaths were also assessed for the period from enrollment to the planned time of infusion to assess risks for subjects who did not receive KTE-X19 due to manufacturing issues or adverse events. Ninety-one subjects were leukapheresed; however, nine subjects (10%) did not receive treatment, seven subjects (8%) were reported dead before infusing, one subject (1%) withdrew, and one subject (1%) developed atrial fibrillation and therefore did not meet criteria for KTE-X19 infusion. For the safety review, "Day 0" refers to the day of KTE-X19 infusion, and some AEs are presented as grouped terms. The applicant used preferred terms and grouped certain terms to present adverse reactions, but the grouping used was limited and occasionally missed cases. For a more comprehensive evaluation of safety, the clinical reviewer's analysis included grouped AEs that represented the same or similar clinical conditions. Examples are listed below. Please refer to Appendix A for the full list of FDA's grouped terms.

- **Delirium:** Agitation, delirium, delusion, disorientation, hallucination, restlessness, irritability, personality change, hypomania
- **Encephalopathy:** Cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia,

somnolence, drowsiness, stupor, lethargy, amnesia, altered state of consciousness

- **Motor dysfunction:** Muscle spasms, muscular weakness, dyskinesia, eyelid ptosis, muscle twitching, intensive care acquired weakness, mobility decreased
- **Pneumonia:** Lung infection, pneumonia, pneumonia klebsiella, pneumonia staphylococcal, lung infiltration

All 82 subjects (100%) had at least one AE. AEs and SAEs are events that occurred after the administration of KTE-X19. Table 31 presents an overview of all AEs.

Table 31. Overview of adverse events in the Safety Analysis Set (SAS; N = 82).

Adverse Events	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
Any AE	68 (100%)	14 (100%)	82 (100%)
Worst grade >/= 3	67 (99%)	13 (93%)	80 (98%)
Any SAE	46 (68%)	8 (57%)	54 (65%)
Worst grade >/= 3	37 (54%)	7 (50%)	44 (53%)
Any CRS*	62 (91%)	13 (93%)	75 (91%)
Worst grade >/= 3	11 (16%)	5 (36%)	15 (18%)
Any Neurotoxicity	52 (77%)	14 (100%)	66 (80%)
Worst grade >/= 3	23 (34%)	7 (50%)	30 (37%)
Fatal AEs excluding progressive disease	2 (3%)	1 (7%)	3 (4%)

AE = adverse event, CRS = cytokine release syndrome, SAE = serious adverse event
Data cutoff 24 July 2019
**CRS events were graded by Lee et al 2014. CRS grading is provided by syndrome level.*
(Source: FDA analysis of applicant dataset ADAE)

Table 32. Serious adverse events by system organ class and preferred term occurring in >/= 10% of subjects.

Body System Organ Class AE	All Grades N (%)	Grades 3 or Higher N (%)
Blood and lymphatic system disorders		
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%)

Body System Organ Class AE	All Grades N (%)	Grades 3 or Higher N (%)
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 conditions		
Fever	77 (94%)	12 (15%)
Fatigue	39 (48%)	2 (2%)
Chills	34 (41%)	0 (0%)
Edema	29 (35%)	2 (2%)
Pain	11 (13%)	2 (2%)
Immune system disorders		
Immunoglobulins decreased	13 (16%)	1 (1%)
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 disorders		
Hypophosphatemia	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		
Musculoskeletal pain**	29 (35%)	1 (1%)
Motor dysfunction	14 (17%)	3 (4%)
Neoplasms benign, malignant		
B cell lymphoma	2 (2%)	2 (2%)
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%)
Dysgeusia	8 (7%)	0 (0%)
Ataxia**	6 (7%)	1 (1%)
Psychiatric disorders		
Delirium**	13 (16%)	4 (5%)
Insomnia	17 (21%)	0 (0%)

Body System Organ Class AE	All Grades N (%)	Grades 3 or Higher N (%)
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 disorders		
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 grouped terms as detailed in Appendix A*

Clinical reviewer comment
The incidence and types of AEs noted after KTE-X19 treatment are of tolerable severity and are consistent with known safety signals reported with other CAR T products. The AEs depicted above reflect not only the toxicities of KTE-X19 but also prior bridging chemotherapy and lymphodepletion. Infections and cytopenias are well-known risks of lymphodepleting chemotherapy and prior conditions as discussed below. Labeling should include appropriate warnings and recommendations regarding monitoring for these AEs. There are acceptable discrepancies between Table 32 in the clinical review, above, and Table 4 in the prescribing information. These discrepancies do not change the overall risk-benefit assessment of the product.

Leukapheresis Period AEs
The Leukapheresis Period was defined from the day of leukapheresis until the day before the start of conditioning chemotherapy. Therefore, this period included collection of AEs that may have resulted from bridging therapy. The leukapheresis population included 91 subjects. Table 33 summarizes the AEs that occurred during the Leukapheresis Period.

Table 33. Selected adverse events during the Leukapheresis Period.

Adverse Events	Subjects N (%)
Any AE	20 (22%)
Neutropenia	7 (8%)
Thrombocytopenia	4 (4%)
Anemia	3 (3%)
Fatigue	2 (2%)
Hypocalcemia	2 (2%)
Leukopenia	2 (2%)
Motor dysfunction	2 (2%)
Pyrexia	2 (2%)
Bacteremia	1 (1%)
Dehydration	1 (1%)
Dizziness	1 (1%)
Hypotension	1 (1%)
Lymphopenia	1 (1%)
Pneumonia	1 (1%)
Pneumonitis	1 (1%)
Sepsis	1 (1%)

(Source: FDA analysis of applicant dataset ADAE)

Grade 3 or higher AEs occurred in nine subjects (10%) and mainly consisted of cytopenias.

Conditioning Chemotherapy Period AEs

The Conditioning Chemotherapy Period was defined from the first day of conditioning chemotherapy until Day -1, the day prior treatment with KTE-X19. The conditioning chemotherapy population included 82 subjects. Table 34 below summarizes the AEs that occurred in this period.

Table 34. Selected adverse events in the Conditioning Chemotherapy Period.

Adverse Events*	Subjects N (%)
Any AE	45 (56%)
Leukopenia	12 (15%)
Neutropenia	9 (11%)
Thrombocytopenia	8 (10%)
Lymphopenia	6 (7%)
Nausea	6 (7%)
Anemia	5 (6%)
Pyrexia	5 (6%)
Diarrhea	3 (4%)
Tachycardia	3 (4%)
Vomiting	3 (4%)
Decreased appetite	2 (2%)
Hyperbilirubinemia	2 (2%)
Hypokalemia	2 (2%)
ALK increased	1 (1%)
Chills	1 (1%)
Edema	1 (1%)
Fatigue	1 (1%)

AE = adverse event, ALK = alkaline phosphatase
** Includes grouped terms as detailed in Appendix A*

(Source: FDA analysis of applicant datasets ADSL and ADAE)

Grade 3 or higher AEs occurred in 15 subjects (18%) and mainly consisted of cytopenias.

6.1.12.3 Deaths

This reviewer reviewed all narratives and case report forms (CRFs) to confirm the reported causes of death. In addition to the narratives themselves, the applicant provided their adjudication of the proximate and/or root cause of the death in each case. FDA considered the cause of death to be the underlying malignancy when supported by worsening of disease by imaging, biopsy, autopsy, or description of other objective evidence. The majority of deaths were due to progressive disease.

In general, there was agreement between the applicant and FDA analyses. The leading cause of death as of the data cutoff was progression of disease (15 subjects, 18%). Five subjects died within three months after KTE-X19 infusion, and 15 subjects died more than three months after KTE-X19 infusion. Three subjects died due to AEs. Deaths that occurred in ZUMA-2 are summarized in Table 35.

Table 35. Summary of deaths observed in ZUMA-2.

Characteristic	Statistics	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
All Deaths		16 (24%)	4 (29%)	20 (24%)
Cause of Death	Progressive Disease	13 (19%)	2 (14%)	15 (18%)
	Adverse event	2 (3%)	1 (7%)	3 (4%)
	Other *	1 (1%)	1 (7%)	2 (2%)
Deaths </= 30 days after KTE-X19		0	1 (7%)	1 (1%)
Deaths > 30 days after KTE-X19		16 (24%)	3 (21%)	19 (23%)

** One subject in Cohort 2 died of HSCT regimen-related toxicity; one subject in Cohort 1 had a cause of death reported as "unknown"*

(Source: FDA analysis of applicant datasets ADSL, DT, and ADAE; individual subject narratives; and CRFs)

Narratives for subjects who died due to an AE or within 30 days of KTE-X19 treatment are detailed below:

Subject (b) (6), a 73-year-old woman in Cohort 1, died due to organizing pneumonia on Day 37. She developed acute respiratory distress and grade 4 respiratory failure on Day 21. Preceding events included acute kidney failure. The subject also experienced CRS, maximum grade 4, from Day 3 to Day 20. The death was deemed related to conditioning chemotherapy but unrelated to KTE-X19.

Clinical reviewer comments
According to information provided in the narrative and review of the SAE report, the subject initially experienced grade 3 CRS and grade 3 neurotoxicity. Over time her clinical condition worsened, leading to critical illness with grade 4 acute kidney injury and acute respiratory distress syndrome (ARDS) that required endotracheal intubation. An infectious disease work-up, including lumbar puncture, was done with negative results. The subject's last labs results showed leukopenia, thrombocytopenia, and anemia. Medical care was withdrawn. Autopsy demonstrated a saddle pulmonary embolus and acute tubular necrosis. The cause of death was organizing pneumonia with contributions from organizing thromboembolism of the lung that caused ARDS. The thromboembolus went undiagnosed as the subject had renal failure and was unable to undergo a CT scan with contrast. It is not certain that both lymphodepletion and KTE-X19 did not contribute to the development of acute kidney injury, thromboembolism, and ARDS.

Subject (b) (6), a 71-year-old male in Cohort 1, died due to staphylococcal bacteremia (methicillin-resistant Staphylococcus aureus) on Day 134 after KTE-X19 infusion. The fatal event was listed as streptococcal bacteremia at the cutoff date. The subject was discharged per his request on Day 132. He died due to sepsis. No autopsy was performed. The death was deemed related to conditioning chemotherapy and KTE-X19.

Clinical reviewer comment
The subject experienced CTCAE grade 3 bacteremia on Day 31 with leukocytes of 2.5 x10^3/ul. Peripheral blood cultures were positive for gram positive Staphylococcus. The source of infection was likely the subject's port-a cath placed prior to enrollment on study. He was treated with IV antibiotics, but his infection did not improve. He developed methicillin-resistant Staphylococcus aureus (MRSA) osteomyelitis with invasion of the spinal discs, and blood cultures remained positive for MRSA despite the antibiotics. The subject decided to discontinue antibiotics and transfer to hospice care. The subject received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (maxi-R-CHOP) alternating with high dose (HD) cytarabine, and then ibrutinib, before entering the study. He was not heavily pretreated and had a low tumor burden. Based on the available information, this reviewer agrees that both lymphodepletion and KTE-X19 played a role in the development of bacteremia and death.

Subject (b) (6), a 64-year-old male in Cohort 2, died on Day 18 from cardiac arrest. This subject was noted to have an elevated anion gap before receiving KTE-X19. The metabolic acidosis and elevated anion gap worsened on Day 6, followed by CRS on Day 10 (which resolved on Day 13) and encephalopathy on Day 12 (which was ongoing as of the date of death).

Clinical reviewer comment
The applicant reported the death of subject (b) (6) as unrelated to study treatment. However, this reviewer could not rule out the possibility that CRS had played a role in the death of this subject, and therefore this information will be included in the label.

Deaths in subjects not treated with KTE-X19:
Nine subjects were leukapheresed and enrolled but not treated with KTE-X19. Refer to 6.1.10.1.3 Subject Disposition within 6.1.10.1 Populations Enrolled/Analyzed.

6.1.12.4 Nonfatal Serious Adverse Events

For this review, SAEs were defined as any serious AE that occurred after the start of KTE-X19 administration. SAEs occurred in 65 of 82 subjects (80%). All subjects were hospitalized for a minimum of seven days per protocol. Twenty-five of 82 subjects (30%) were admitted to the intensive care unit (ICU). Table 36 summarizes all SAEs and grade >/= 3 SAEs.

Table 36. Nonfatal serious adverse events.

Adverse Events*	All Grades N (%)	Grades 3 or Higher N (%)
Encephalopathy	26 (32%)	19 (23%)
Pyrexia	19 (23%)	5 (6%)
Hypotension	14 (17%)	11 (13%)
Pneumonia	12 (15%)	12 (15%)
Hypoxia	10 (12%)	10 (12%)
Arrhythmia	8 (10%)	6 (7%)
Renal insufficiency	8 (10%)	8 (10%)
Anemia	6 (7%)	6 (7%)
Respiratory failure	6 (7%)	6 (7%)
Aphasia	5 (6%)	5 (6%)
B-cell lymphoma	5 (6%)	5 (6%)
Dyspnea	5 (6%)	4 (5%)
Sepsis	5 (6%)	5 (6%)
Thrombosis	5 (6%)	4 (5%)
Bacterial infection	4 (5%)	4 (5%)
Pleural effusion	4 (5%)	3 (4%)
Thrombocytopenia	4 (5%)	4 (5%)
Bacteremia	3 (4%)	3 (4%)
Hypertransaminasemia	3 (4%)	3 (4%)
Tachycardia	3 (4%)	0 (0%)
Tumor lysis syndrome	3 (4%)	3 (4%)
Dehydration	2 (2%)	1 (1%)
Diarrhea	2 (2%)	2 (2%)
Dizziness	2 (2%)	2 (2%)
Fatigue	2 (2%)	0 (0%)
Hypertension	2 (2%)	2 (2%)
Motor dysfunction	2 (2%)	2 (2%)
Musculoskeletal pain	2 (2%)	2 (2%)
Neutropenia	2 (2%)	2 (2%)
Seizure	2 (2%)	1 (1%)
Viral infection	2 (2%)	1 (1%)

** Includes grouped terms as detailed in Appendix A*

(Source: FDA analysis of applicant dataset ADAE)

The most common were encephalopathy, pyrexia, hypotension, pneumonia, hypoxia, and arrhythmias.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest for safety analyses included cytokine release syndrome, neurotoxic events, and prolonged cytopenias.

Cytokine release syndrome (CRS)
CRS and CRS symptoms occurred in 75 subjects (91%), 18% of whom experienced grade 3 or higher CRS. Among subjects who died after receiving KTE-X19, one had CRS at the time of death (see 6.1.12.3 Deaths for details).

The median time to onset of CRS was three days (range 0 to 12 days), and the median time to resolution of CRS was 13 days (range 1 to 50 days). The median time to peak CRS severity was five days (range 0 to 11 days).

Manifestations of CRS included fever, hypotension, hypoxia, tachycardia, and chills. Serious events that may be associated with CRS include hypotension, hypoxia, acute kidney injury, cardiac arrhythmias including atrial fibrillation, ventricular tachycardia, cardiac arrest, and cardiac failure. CRS was graded per modified Lee et al 2014 criteria, which excludes neurologic AEs as part of CRS. The majority of CRS symptoms resolved at the time of the data cutoff except for one subject, who had ongoing CRS at the time of death. Table 37 below summarizes the observed CRS.

Table 37. Cytokine release syndrome in ZUMA-2.

Characteristic	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
Any CRS	62 (91%)	13 (93%)	75 (91%)
>/= Grade 3 CRS	11(16%)	4 (29%)	15 (18%)
Median time to onset (range) in days	1 (0-12)	5 (0-10)	3 (0-12)
Median time to peak (range) in days	3 (0-11)	9 (5-10)	5 (0-11)
Median time to resolution	12 (1-50)	15 (6-30)	13 (1-50)

Clinical reviewer comment
The applicant's definition of CRS duration was "the number of days from the first onset of CRS syndrome to the last stop date of CRS syndrome, with the non-event date in between subtracted (ie: [stop date of last CRS – start date of first CRS +1] – number of non-event days in between)". This definition is not acceptable, because in many instances, while reviewing the CRFs and subjects' narratives, this reviewer confirmed that certain individual CRS symptoms in some subjects remained despite the investigator's or applicant's claim that CRS had resolved. Therefore, for the purpose of this review, CRS duration was calculated without subtracting the non-event days in between. CRS duration was calculated based on the earliest day the event began in the study period and the final study day that the event was noted. This analysis includes the subjects who were retreated with KTE-X19.

Table 38. CRS toxicity grades.

Characteristic	Cohort 1 N = 62	Cohort 2 N = 13	Overall N = 75
Grade 1 n (%)	20 (32%)	2 (15%)	22 (29%)
Grade 2 n (%)	31 (50%)	7 (54%)	38 (51%)
Grade 3 n (%)	5 (8%)	2 (15%)	7 (9%)
Grade 4 n (%)	6 (10%)	1 (8%)	7 (9%)
Grade 5 n (%)	0 (0%)	1 (8%)	1 (1%)

(Source: FDA analysis of applicant datasets ADAE and XC)

Clinical reviewer comment
This reviewer found discrepancies in the CRS grading between the datasets, narratives, and CRFs for the following subjects:

Subject (b) (6): This subject was reported to have CRS grade 3 from Day 5 to Day 16. The narrative, CRF, and MedWatch report document hypoxia grade 4 (intubated) on Day 8. The subject received IV fluids, tocilizumab, dexamethasone, norepinephrine, and phenylephrine to treat CRS. The investigator assessed the event of respiratory failure as grade 4, and we cannot rule out that respiratory failure may have been due to CRS. The applicant reported an alternative etiology for respiratory failure as "unknown."

Clinical reviewer comment
Given grade 4 respiratory failure requiring mechanical ventilation and no alternative etiology, CRS grade changed to grade 4.

Subject (b) (6): This subject developed CRS grade 3 from Day 3 to Day 20. The applicant considered the initial event resolved on Day 10 because on Day 10 the subject was weaned from high oxygen requirements. The subject subsequently experienced increasing oxygen requirements and worsening chest X-ray findings which then required mechanical ventilation for grade 4 respiratory failure. Complete infectious work-up was reported negative. The subject developed acute kidney injury (AKI) on Days 32 to 37 and died on Day 37. Autopsy revealed no neoplasm seen; pulmonary edema, pleural effusions, and pericardial effusion.

Clinical reviewer comment
Considering the initial CRS event resolved on Day 10 is not accurate. The subject's clinical respiratory symptoms continued to deteriorate, with increasing oxygen requirements and ultimately intubation. Pneumonia is a generic term and has several etiologies, including CRS. Our review indicates that CRS was not resolved on Day 10 and the subject had respiratory and renal failure that could be explained by CRS. Therefore, CRS should be graded as grade 4.

Subject (b) (6) This subject developed CRS grade 3 from Day 1 to Day 12 and hypotension Day 0 to 12. The subject's baseline creatinine was 0.7 mg/dL documented on Day 2, and it increased to 1.1 mg/dL and 1.8 mg/dL on Day 6 and Day 7, respectively. The subject was treated with paracentesis on Day 8 and developed AKI from Day 9 to Day 18.

Clinical reviewer comment

CRS played a role in the development of AKI which is grade 4 by CTCAE v 4.0. Therefore, CRS per Lee criteria, which considers organ toxicity for grading purposes, is grade 4.

Subject (b) (6) : This subject experienced an SAE of grade 3 hypotension from Day 5 to Day 9 and received continuous norepinephrine infusion on Day 6 to Day 8 (5 mcg/min), tocilizumab on Day 5 to Day 6, siltuximab on Day 7, and methylprednisolone on Day 7 to Day 12. The subject developed grade 3 pleural effusion (Day 6 to day 16) and grade 3 pulmonary edema (Day 6 to Day 16). The subject developed hypoxia requiring oxygen high flow nasal canula (HFNC) with 60% Fi02 on Day 6.

Clinical reviewer comment
CRS was upgraded from grade 2 to grade 3 based on pulmonary organ toxicity and oxygen requirement of > 40% FiO2.

Subject (b) (6) This subject developed grade 2 CRS on Day 11 and subsequently required mechanical ventilation for hypoxia.

Clinical reviewer comment
The subject required mechanical ventilation, hence CRS was upgraded to grade 4.

Subject (b) (6) : This subject was reported to have grade 2 CRS, grade 3 neurotoxicity, metabolic acidosis, and finally cardiac arrest on Day 18. The subject had progressive respiratory failure, worsening pulmonary radiographic findings, worsening renal function, cardiac arrythmias, and finally cardiac arrest.

Clinical reviewer comment
This subject had respiratory failure, worsening renal function, cardiac arrythmias, and finally cardiac arrest. This reviewer did not agree with the applicant's assigned grade 2 CRS. Based on respiratory and kidney failure, cardiac arrythmias, and cardiac failure, CRS was upgraded to grade 5.

The most common CRS symptoms included fever, hypotension, hypoxia, chills, and tachycardia. Table 39 presents individual and grade >/= 3 CRS symptoms.

Table 39. CRS individual symptoms grade >/= 3 (N = 82).

CRS AEs*	**All Grades N (%)**	**Grades 3 or Higher N (%)**
Pyrexia	74 (90%)	10 (12%)
Hypotension	45 (55%)	21 (26%)
Hypoxia	28 (34%)	14 (17%)
Chills	25 (30%)	0 (0%)
Tachycardia	21 (26%)	0 (0%)
Headache	18 (22%)	0 (0%)
Fatigue	12 (15%)	1 (1%)
ALT increased	10 (12%)	4 (5%)
Nausea	10 (12%)	0 (0%)
AST increased	9 (11%)	5 (6%)

CRS AEs*	All Grades N (%)	Grades 3 or Higher N (%)
Diarrhea	8 (10%)	2 (2%)
Sinus tachycardia	8 (10%)	0 (0%)
Dyspnea	6 (7%)	2 (2%)
Atrial fibrillation	4 (5%)	1 (1%)
Myalgia	4 (5%)	0 (0%)
C-reactive protein increased	3 (4%)	1 (1%)
Malaise	3 (4%)	0 (0%)
Acute kidney injury	2 (2%)	2 (2%)
Pulmonary edema	2 (2%)	1 (1%)
Vomiting	2 (2%)	0 (0%)
Arthralgia	1 (1%)	0 (0%)
Asthenia	1 (1%)	0 (0%)
Atrial flutter	1 (1%)	1 (1%)
Blood ALK increased	1 (1%)	0 (0%)
Dizziness	1 (1%)	0 (0%)
EKG T-wave amplitude increased	1 (1%)	0 (0%)
Hyperbilirubinemia	1 (1%)	1 (1%)
Hypophosphatemia	1 (1%)	1 (1%)
Influenza like illness	1 (1%)	0 (0%)
Multiple organ dysfunction syndrome	1 (1%)	1 (1%)
Neutropenia	1 (1%)	1 (1%)
Pleural effusion	1 (1%)	1 (1%)
Presyncope	1 (1%)	0 (0%)
Pulmonary congestion	1 (1%)	0 (0%)
Rash	1 (1%)	0 (0%)
Rash maculo-papular	1 (1%)	1 (1%)
Rash pustular	1 (1%)	1 (1%)
Respiratory rate increased	1 (1%)	0 (0%)
Serum ferritin increased	1 (1%)	1 (1%)
Shock	1 (1%)	0 (0%)
Supraventricular tachycardia	1 (1%)	0 (0%)
Transaminases increased	1 (1%)	1 (1%)
Tremor	1 (1%)	0 (0%)
Troponin increased	1 (1%)	0 (0%)
Ventricular arrhythmia	1 (1%)	0 (0%)

ALK = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, EKG = electrocardiogram
** Not including grouped terms*

(Source: FDA analysis of applicant datasets ADAE and XC)

Table 40. CRS serious adverse events (SAEs) (N=82).

CRS AEs*	All Grades N (%)	Grades 3 or Higher N (%)
Hypotension	13 (16%)	10 (12%)
Pyrexia	12 (15%)	3 (4%)
Hypoxia	8 (10%)	7 (9%)
Acute kidney injury	2 (2%)	2 (2%)
Tachycardia	2 (2%)	0 (0%)
ALT increased	1 (1%)	1 (1%)
AST increased	1 (1%)	1 (1%)
Atrial fibrillation	1 (1%)	1 (1%)
Atrial flutter	1 (1%)	1 (1%)
CRP increased	1 (1%)	1 (1%)
Diarrhea	1 (1%)	1 (1%)
Dyspnea	1 (1%)	1 (1%)
Malaise	1 (1%)	0 (0%)
Multiple organ dysfunction syndrome	1 (1%)	1 (1%)
Neutropenia	1 (1%)	1 (1%)
Pleural effusion	1 (1%)	1 (1%)
Pulmonary edema	1 (1%)	1 (1%)
Rash pustular	1 (1%)	1 (1%)
Serum ferritin increased	1 (1%)	1 (1%)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C-reactive protein
** Not including grouped terms*

(Source: FDA analysis of applicant datasets ADAE and XC)

Of the 75 subjects who had CRS events, two subjects received a second treatment with KTE-X 19. When indicated, these subjects were considered as separate subjects. Both subjects had CRS grade 1 after re-treatment. The majority of CRS symptoms had resolved at the time of the data cutoff, except for the one subject who had a CRS event at the time of death.

Clinical reviewer comment
Overall this reviewer agreed with the applicant's classification of CRS; however, this reviewer identified discrepancies in the CRS grading. These discrepancies were communicated to the applicant, who agreed to modify CRS grading for those subjects. The changes did not affect the conclusions regarding CRS related to KTE-X19.

Neurotoxicity
FDA's neurotoxicity analysis was based on the MedDRA system organ classes and included all events from the nervous system disorders and psychiatric disorders that occurred, regardless of the applicant's attribution as "neurological flag". The analyses captured events misclassified under other organ system classes and not captured by the applicant as neurologic (e.g., five ataxia events were classified as gait disturbance under

"General disorders"). For the purpose of this review, certain AEs were grouped into a larger category (e.g., encephalopathy, delirium).

Sixty-six subjects (81%) experienced one or more neurotoxicity events. Thirty subjects (37%) experienced grade 3 or higher events, and the most common serious grade 3 or higher event was encephalopathy.

The following neurotoxicity events occurred in >/= 10% of subjects: encephalopathy, tremor, headache, aphasia, delirium, dizziness, neuropathy, and ataxia. A total of 66 subjects experienced one or more of these events. These neurologic events of special interest (NESI) are a cluster of neurological symptoms or signs that are associated with immunotherapies primarily based on what is known in the field and in the scientific literature available.

The median time to onset of any neurotoxicity was five days (range 0 to 31 days). The median duration was 21 days. Although the median time to resolution was 28 days, prolonged grade 3 encephalopathy was noted up to 187 days post-infusion (maximum duration of 180 days (subject ID (b) (6)) and grade 1 dizziness was noted up to 174 days (maximum duration of 162 days) post-infusion.

The median time to onset of neurotoxicity grade 3 or higher was three days, and the median duration was 26 days. Please see the tables below for data on neurotoxicity.

Table 41. Neurotoxicity.

Characteristic	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
Any neuropsychiatric event (NE)	52 (77%)	14 (100%)	66 (81%)
>/= Grade 3 NE	23 (34%)	7 (50%)	30 (37%)
Median time to onset (range) in days	5 (0-31)	6 (0-15)	5 (0-31)
Median time to peak (range) in days	7 (2-441)	15 (7-33)	2 (2-441)
Median time to resolution	28 (6-571)	36 (14-470)	28 (6-571)

(Source: FDA analysis of applicant datasets ADAE, ADSL, and ADSAF)

Clinical reviewer comments
The clinical review team defined the term "encephalopathy" based on literature review. Encephalopathy was grouped based on the following terms: cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, drowsiness, stupor, lethargy, amnesia, and altered state of consciousness. The applicant did not provide a definition for encephalopathy and instead listed the above symptoms individually. Therefore, the incidence of encephalopathy in this review is higher than that the applicant reported.

The term "gait disturbance", which is under "General disorders and administration site conditions", was grouped by FDA analysis with the term "ataxia".

Table 42. Subjects' neurologic events (all AEs)*.

Characteristic	Cohort 1 N = 68 n (%)	Cohort 2 N = 14 n (%)	Overall N = 82 n (%)
N (%)	**52 (77%)**	**14 (100%)**	**66 (81%)**
Encephalopathy	32 (47%)	9 (64%)	41 (50%)
Tremor	24 (35%)	7 (50%)	31 (38%)
Headache	24 (35%)	5 (36%)	29 (35%)
Aphasia	13 (19%)	6 (43%)	19 (23%)
Anxiety	10 (15%)	4 (29%)	14 (17%)
Dizziness	9 (13%)	4 (29%)	14 (16%)
Delirium	9 (13%)	4 (29%)	13 (16%)
Neuropathy	8 (12%)	4 (29%)	12 (15%)
Ataxia	6 (9%)	0 (0%)	6 (7%)
Vision blurred	4 (6%)	2 (14%)	6 (7%)
Seizure	4 (6%)	0 (0%)	4 (5%)
Depression	3 (4%)	1 (7%)	4 (5%)
Diplopia	2 (3%)	0 (0%)	2 (2%)
Dysgeusia	2 (3%)	1 (7%)	3 (4%)
Tinnitus	2 (3%)	0 (0%)	2 (2%)
Papilledema	1 (1%)	0 (0%)	1 (1%)
Autoscopy	1 (1%)	0 (0%)	1 (1%)
Motor dysfunction	1 (1%)	0 (0%)	1 (1%)
Hypomania	1 (1%)	0 (0%)	1 (1%)
Brain edema	1 (1%)	0 (0%)	1 (1%)
Nystagmus	1 (1%)	1 (7%)	2 (2%)
Dysgraphia	0 (0%)	1 (7%)	1 (1%)
Neurotoxicity	0 (0%)	1 (7%)	1 (1%)
Migraine	0 (0%)	1 (7%)	1 (1%)

** Includes grouped terms as detailed in Appendix A*

(Source: FDA analysis of applicant dataset ADAE)

Table 43. Neuropsychiatric symptoms grade >/= 3.

Neuropsychiatric Symptoms Grade >/= 3	Subjects N (%)
Any NE G >/= 3	30 (37%)
Encephalopathy	19 (23%)
Aphasia	7 (9%)
Delirium	4 (5%)
Dizziness	2 (2%)
Neuropathy	2 (2%)
Syncope	2 (2%)
Tremor	2 (2%)
Ataxia	1 (1%)
Brain edema	1 (1%)
Dysgraphia	1 (1%)
Headache	1 (1%)
Intensive care unit acquired weakness	1 (1%)
Neurotoxicity	1 (1%)
Seizure	1 (1%)

** Includes grouped terms as detailed in Appendix A*

(Source: FDA analysis of applicant dataset ADAE)

Table 44. Neurotoxicity grades.

Worst Neurotoxicity Grade	Subjects N (%)
Any toxicity grade	**66 (80%)**
Grade 1	57 (35%)
Grade 2	46 (56%)
Grade 3	26 (31%)
Grade 4	6 (7%)

(Source: FDA analysis of applicant dataset ADAE)

One subject had brain edema that was non-fatal, and the most common grade 3 NEs were encephalopathy, aphasia, delirium, and dizziness. Distribution of neurotoxicity events of special interest by grades and types of neurotoxicity are listed in Table 45.

Table 45. NESI distribution by maximum toxicity grade in the Safety Analysis Set (N = 82).

FDA Grouped Term	Grade 1	Grade 2	Grade 3	Grade 4
Anxiety	9 (11%)	5 (6%)	0 (0%)	0 (0%)
Aphasia	6 (7%)	6 (7%)	7 (9%)	0 (0%)
Ataxia	1 (1%)	4 (5%)	1 (1%)	0 (0%)
Brain edema	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Delirium	4 (5%)	5 (6%)	4 (5%)	0 (0%)
Dizziness	9 (11%)	2 (2%)	2 (2%)	0 (0%)
Dysgraphia	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Encephalopathy	9 (11%)	13 (16%)	13 (16%)	6 (7%)
Headache	18 (22%)	10 (12%)	1 (1%)	0 (0%)
Neuropathy	9 (11%)	1 (1%)	2 (2%)	0 (0%)
Papilledema	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Tremor	20 (24%)	9 (11%)	2 (2%)	0 (0%)
Vision blurred	5 (6%)	1 (1%)	0 (0%)	0 (0%)
Subjects	**57 (35%)**	**46 (56%)**	**28 (34%)**	**6 (7%)**

Table 46 summarizes selected neurotoxicity events of special interest of any grade. One subject may have experienced more than one grade of events.

Table 46. NESI distribution by toxicity grade (N = 66)*.

FDA Term	Grade 1	Grade 2	Grade 3	Grade 4
Anxiety	11	5	0	0
Aphasia	13	11	7	0
Ataxia	2	6	1	0
Brain edema	0	0	0	1
Delirium	5	6	4	0
Dizziness	15	3	2	0
Dysgeusia	2	2	0	0
Dysgraphia	0	0	1	0
Encephalopathy	58	40	23	6
Headache	33	14	1	0
Neuropathy	12	2	2	0
Nystagmus	0	2	0	0
Papilledema	1	0	0	0
Syncope	0	0	2	0
Tremor	32	10	3	0
Vision blurred	5	1	0	0
Total Events	**189**	**102**	**46**	**7**

**66 of the 82 safety evaluable subjects experienced NESI*

Table 47. Unresolved neurotoxicity events at data cutoff*.

Cohort	Subject	Preferred Term	FDA GT	CTCAE Grade	Start Study Day	End Study Day	Duration in Days
1	(b) (6)	Disturbance in attention	Encephalopathy	2	8	288*	84
		Headache	Headache	3	35	288*	253
		Tremor	Tremor	1	8	288*	280
		Tremor	Tremor	1	35	241	206
		Tremor	Tremor	1	11	205	194
		Agitation	Delirium	2	0	37**	38
		Hyperalgesia	Neuropathy	2	37	134**	98
		Dysesthesia	Neuropathy	1	31	80	49
		Hypomania	Hypomania	2	44	57	13
2		Tremor	Tremor	15	1	429*	415
		Encephalopathy	Encephalopathy	3	12	18**	4
		Confusional state	Encephalopathy	2	15	18	3
		Tremor	Tremor	1	15	429*	415
		Tremor	Tremor	1	15	484*	470

CTCAE: Common Terminology Criteria for Adverse Events v 4.03, FDA GT = FDA grouped term
** Ongoing at the time of data cutoff*
*** Death*

Clinical reviewer comment
The applicant reports that subject (b) (6) *had unresolved grade 1 memory impairment that started before IP infusion (AESTDY -4) and resolved on the day of infusion (AEDY 0), followed by a second memory loss that started on Day 261. This reviewer did not include this subject among the unresolved NE.*

Relationship between neuropsychiatric events and CRS events
To evaluate the relationship of neurotoxicities to CRS, neurotoxic events of special interest that occurred within 60 days were used in this analysis. This is because some of the neurotoxicities occurred late and were isolated (e.g., transient dizziness occurred 175 days post-infusion and were considered by FDA as not related to the product). For analysis purposes, subjects who received a second infusion and experienced CRS and/or neurotoxicities after the second infusion were considered to have events separate from those occurring following the first infusion.

There were 66 subjects who had neurotoxicity events with onset that occurred within 60 days of KTE-X19 infusion, and 68 subjects when counting subjects who received a second infusion separately.

Eighty subjects experienced a total of 82 CRS and/or neurotoxicity events (two of the 82 events of CRS and/or neurotoxicity occurred in subjects who received a second infusion). Of the 80 subjects, 14 (18%) experienced only CRS events with no neurotoxicity. Five (6%) subjects experienced neurotoxicity events without CRS. A total of 61 (76%) subjects experienced both CRS and neurotoxicity. Of these, 89% (54 of 61) experienced neurotoxicity events that occurred after CRS onset, and 18% (11 of 61)

experienced neurotoxicity events before CRS onset. Eight subjects had neurotoxicities that began after CRS had resolved. Therefore, 87% (53 of 61) of neurotoxicities occurred during CRS events.

Figure 3 illustrates the relationship between and time courses of CRS and neurotoxicity.

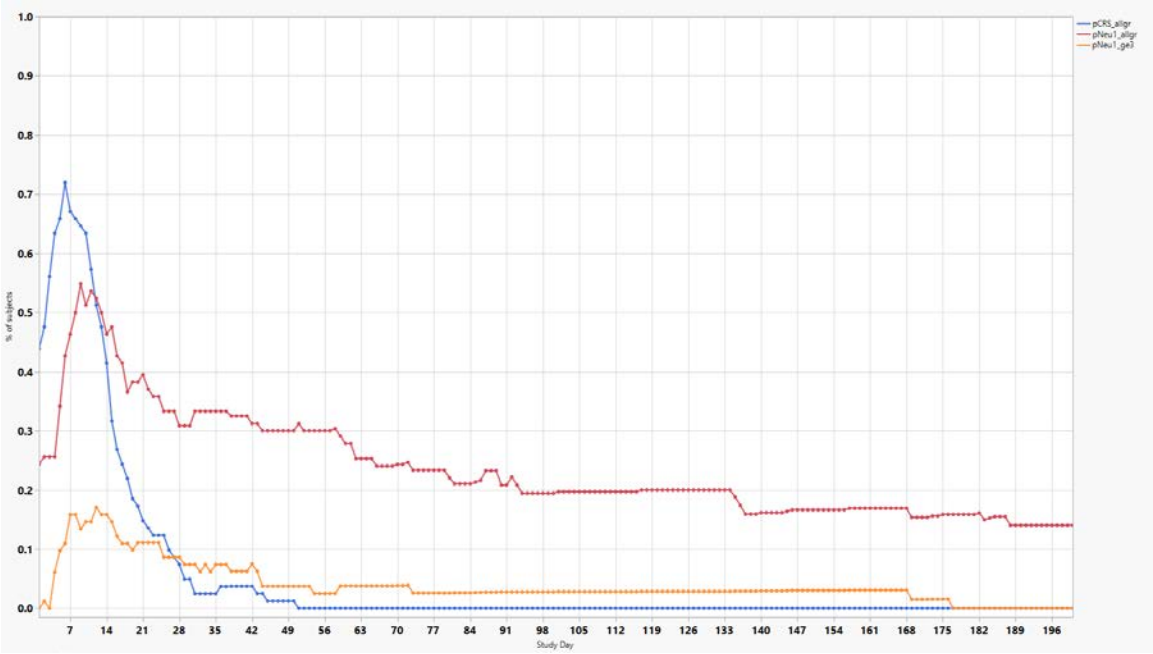

Figure 3. Time courses of CRS and neurotoxicity.
(Source FDA analysis of applicant datasets ADSAE, ADAE, and XC using SAS)

Clinical reviewer comment
The duration of neurotoxicity was calculated based on the earliest date of onset and the final end date for any of the neurologic events that were grouped under the neurologic events of special interest (NESI). The duration of NESI should be interpreted with caution, keeping this caveat in mind. In some subjects the duration of NESI appears prolonged, and these "outliers" were the result of persistent but less serious clinical events such as anxiety and/or tremors.

Concomitant medications

Concomitant medications are medications that were started following the first dose of KTE-X19 and prior to hospital discharge. Table 48 summarizes concomitant medications used in ZUMA-2.

Table 48. Concomitant medications.

Medication	Cohort 1 (N= 68) n (%)	Cohort 2 (N=14) n (%)	Overall (N=82) n (%)
Steroids			
Any	42 (62%)	11 (79%)	53 (65%)
To manage CRS	15 (22%)	5 (36%)	20 (24%)
To manage neurologic events	28 (41%)	7 (50%)	35 (43%)
Other use	14 (21%)	5 (36%)	19 (23%)
Tocilizumab			
Any	49 (72%)	11 (79%)	60 (73%)
To manage CRS	41 (60%)	10 (71%)	51 (62%)
To manage neurologic events	18 (26%)	1 (7%)	19 (23%)
Other use	8 (12%)	3 (21%)	11 (13%)
Steroids or tocilizumab	52 (63%)	11 (79%)	63 (77%)
Steroids and tocilizumab	39 (57%)	8 (6%)	47 (57%)
Vasopressor			
Any	15 (22%)	7 (50%)	22 (27%)
To manage CRS	11 (16%)	6 (43%)	17 (23%)
To manage neurologic events	21 (31%)	1 (7%)	22 (27%)
Other use	3 (4%)	2 (3%)	5 (6%)
Immunoglobulins			6 (7%)
Other immunosuppressive agents*			7 (9%)

**Siltuximib was used to manage neurologic events (NE) in three subjects and CRS in one subject. Anakinra (interleukin 1 [IL1] receptor antagonist) was used to manage CRS in one subject. Thymoglobulin was used to manage NE in one subject.*

(Source: FDA analysis of applicant datasets ADCM and ADHO)

Clinical reviewer comments

The grouped term used by the applicant to classify the categories of steroids and v asopressors was reviewed and seems consistent with current practices to treat CRS and NE.

The attribution of concomitant medication use for management of CRS versus neurotoxicity was determined by the applicant.

Table 49. Tocilizumab use by CRS toxicity grade.

Medication	Total Use	Toxicity Grade	Subjects N (%)
Tocilizumab	**51 (62%)**	Grade 1	8 (10%)
		Grade 2	28 (34%)
		Grade 3	8 (10%)
		Grade 4	7 (9%)

(Source: FDA analysis of applicant datasets XC and ADCM)

Of the 60 subjects who received tocilizumab, 35 (58%) subjects received one dose; 13 (22%) subjects received two doses; five (8%) subjects received three doses; four (7%) subjects received four doses; and one (2%) subject each received six, eight, and twelve doses.

Clinical reviewer comment
The protocol-specified dose and frequency of tocilizumab administration is consistent with the prescribing information (PI) for tocilizumab. A maximum of three doses of tocilizumab in a 24-hour period was administered every eight hours with a maximum of four doses. The proposed PI will be consistent with the doses prescribed in ZUMA-2 and in the PI for tocilizumab.

Table 50. Infection incidence by high level grouped term.

High Level Grouped Term	**Any Grade N (%)**	**Grade >/= 3 N (%)**
Infections - pathogen unspecified	34 (43%)	20 (24%)
Viral infectious disorders	14 (17%)	3 (4%)
Bacterial infectious disorders	11 (13%)	5 (6%)
Fungal infections disorders	7 (9%)	0 (0%)
All Infections	47 (57%)	26 (32%)

(Source: FDA analysis of applicant dataset ADAE)

Infection
Infection of any grade occurred in 57% of subjects, and grade 3 or higher occurred in 32% of subjects.

Grade 3 or higher infections included in this review are summarized in Table 51.

Table 51. Infections grade >/= 3.

High Level Grouped Term	High Level Term	Subjects N (%)
Infections - pathogen unspecified	Lower respiratory tract and lung infections	10 (12%)
	Sepsis, bacteremia, viremia and fungaemia NEC	4 (5%)
	Bone and joint infections	2 (2%)
	Dental and oral soft tissue infections	2 (2%)
	Infections NEC	2 (2%)
	Skin structures and soft tissue infections	2 (2%)
	Urinary tract infections	2 (2%)
	Abdominal and gastrointestinal infections	1 (1%)
	Muscle and soft tissue infections	1 (1%)
	Upper respiratory tract infections	1 (1%)
Bacterial infectious disorders	Enterococcal infections	2 (2%)
	Staphylococcal infections	2 (2%)
	Bacterial infections NEC	1 (1%)
	Streptococcal infections	1 (1%)
Viral infectious disorders	Enteroviral infections NEC	1 (1%)
	Herpes viral infections	1 (1%)
	Parvoviral infections	1 (1%)
	Rhinoviral infections	1 (1%)
Skin and subcutaneous tissue disorders NEC	Skin and subcutaneous tissue ulcerations	1 (1%)

(Source: FDA analysis of applicant dataset ADAE)

Prolonged cytopenias >/= 30 days

Fever and neutropenia occurred in 6% of subjects, and grade >/= 3 occurred in 32% of all subjects. Table 52 lists prolonged cytopenia events which lasted longer than 30 days.

Table 52. Prolonged cytopenias grade >/= 3.

FDA Grouped Terms	Subjects N (%)
Any prolonged cytopenia grade >/= 3	**46 (56%)**
Thrombocytopenia	43 (53%)
Neutropenia*	39 (47%)
Anemia	14 (17%)

**Febrile neutropenia occurred in five subjects (6%)*

(Source: FDA analysis of applicant datasets ADAE and ISS)

B cell aplasia

Grade 1 or 2 hypogammaglobulinemia occurred in 12 (15%) subjects. Grade >/= 3 hypogammaglobulinemia was observed in one subject.

Secondary malignancies

To date, there are no reports of secondary malignancies in any subject in the ongoing long-term follow-up study.

Cardiac toxicity

Table 53. Cardiac disorders.

FDA Grouped Terms	Subjects N (%)
Any cardiac disorder	**60 (73%)**
Tachycardia	38 (46%)
Arrhythmia	18 (22%)
Cardiac arrest	1 (1%)
Cardiac failure	1 (1%)
Palpitations	1 (1%)

Table 54. Cardiac disorders grade >/= 3.

FDA Grouped Terms	Subjects N (%)
Any cardiac disorder grade >/= 3	**15 (18%)**
Arrhythmia	8 (10%)
Cardiac arrest	1 (1%)
Cardiac failure	1 (1%)
Cardiomyopathy	1 (1%)
Palpitations	1 (1%)

(Source: FDA analysis of applicant dataset ADAE)

A grade 4 cardiac event was observed in one subject (arrhythmia), as well as one grade 5 cardiac arrest under cardiac disorders. However, the following subjects developed cardiac failure: (b) (6) both had arrhythmias and developed pulmonary edema, while (b) (6) had tachycardia and then developed ejection fraction decreased. Those events were captured under the system organ classes "Respiratory, Thoracic, and Mediastinal" and "Investigations".

Renal toxicity

Renal insufficiency was seen in 15 of the 82 (18%) subjects based on the FDA grouped term that included clinical presentation and laboratory values, and grade >/= 3 in seven (9%) subjects. Four (5%) subjects experienced kidney injury that required dialysis.

Respiratory failure
Six subjects required endotracheal intubation or mechanical ventilation for the management of respiratory failure.

Hospitalization
The protocol required mandatory hospitalization on the day of KTE-X19 infusion and for a minimum of seven days post infusion. The median duration of hospitalization was 16 days (range 7 to 93 days; 95% CI 18, 24). Fifteen (18%) and two (3%) subjects in the safety population remained hospitalized on Days 14 and 21, respectively.

6.1.12.6 Clinical Test Results

The table below summarizes common (occurring in more than 10% of subjects) treatment-emergent hematologic laboratory abnormalities in the safety population.

Table 55. Treatment-emergent hematologic laboratory abnormalities occurring in >/= 10% of subjects.

Hematology Laboratory Abnormality	Cohort 1 N=68		Cohort 2 N=14		Overall N=82	
	All Grades N (%)	Grades >/= 3 N (%)	All Grades N (%)	Grades >/= 3 N (%)	All Grades N (%)	Grades >/= 3 N (%)
Leukopenia	66 (97%)	65 (96%)	14 (100%)	13 (93%)	80 (98%)	78 (95%)
Neutropenia	65 (96%)	64 (94%)	14 (100%)	14 (100%)	79 (96%)	78 (95%)
Thrombocytopenia	64 (94%)	42 (62%)	14 (100%)	11 (79%)	78 (95%)	53 (65%)
Lymphopenia	59 (88%)	56 (84%)	14 (100%)	14 (100%)	73 (90%)	70 (86%)
Anemia	66 (97%)	37 (54%)	13 (93%)	7 (50%)	79 (96%)	44 (54%)

(Source: FDA analysis of adlb.xpt and adsl.xpt)

Cytopenias of all grades were common during treatment, with the most common cytopenias, leukopenia and neutropenia, reported in 98% and 95%, respectively, at any grade, and in 95% when greater than grade 3. Cytopenias as assessed by laboratory data were more frequent than those reported as AEs (“Blood and lymphatics” plus “Investigations”).

Lymphocytosis was reported in 44% of patients with mantle cell lymphoma.

Table 56. Treatment-emergent biochemical laboratory abnormalities.

Laboratory chemistry abnormalities	Cohort 1 N=68		Cohort 2 N=14		Overall N=82	
	All Grades	Grades >/= 3	All Grades	Grades >/= 3	All Grades	Grades >/= 3
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Hypocalcemia	60 (88%)	12 (18%)	14 (100%)	5 (36%)	74 (90%)	17 (21%)
Hypophosphatemia	56 (82%)	21 (31%)	11 (85%)	4 (31%)	67 (83%)	25 (31%)
ALT Increased	51 (75%)	10 (15%)	10 (71%)	2 (14%)	61 (74%)	12 (15%)
Hyperglycemia	51 (75%)	3 (4%)	10 (71%)	2 (14%)	61 (74%)	5 (6%)
AST Increased	47 (69%)	10 (15%)	8 (57%)	2 (14%)	55 (67%)	12 (15%)
Hypokalemia	32 (47%)	7 (10%)	6 (43%)	1 (7%)	38 (46%)	8 (10%)
Hyperbilirubinemia	28 (41%)	1 (2%)	9 (64%)	0 (0%)	37 (45%)	1 (1%)
Creatinine Increased	15 (22%)	4 (6%)	2 (14%)	1 (7%)	17 (21%)	5 (6%)

(Source: FDA analysis of adlb.xpt and adsl.xpt.)

The most common chemistry abnormalities by analysis of laboratory values were hypophosphatemia and hypocalcemia, with 31% and 21% greater than or equal to grade 3, respectively.

Clinical reviewer comments
Laboratory chemistry abnormalities were generally low grade and occurred commonly. Although there was no specific laboratory chemistry pattern indicative of a specific toxicity, since chemistry abnormalities may be related to infectious or tumor-related complications, elevated ALT, bilirubin, and uric acid should be included in the PI to adequately inform providers. Routine laboratory monitoring is recommended.

*The laboratory abnormalities are more detailed in the laboratory dataset as compared to the AE dataset. Therefore, the label will include a separate table for laboratory abnormalities that are derived from the new ADLB dataset***.**

6.1.12.7 Dropouts and/or Discontinuations

Among the 91 subjects who were enrolled in ZUMA-2 and underwent leukapheresis, 84 subjects received the conditioning regimen and 82 subjects were treated with KTE-X19. Of the nine subjects who did not receive KTE-X19, four subjects died prior to KTE-X19, one subject withdrew from the study, one subject developed atrial fibrillation and therefore became ineligible for the study, and three subjects experienced AEs likely related to the disease [deep vein thrombosis (DVT), bacterial and viral infections (which occurred in a subject treated with the conditioning regimen) and tumor lysis syndrome (after a manufacturing failure, before attempting a second leukapheresis)]. The primary reason for study discontinuation following KTE-X19 was death (refer to Table 29 in 6.1.12.1 Methods).

6.1.13 Study Summary and Conclusions

Efficacy: Please refer to 1 Executive Summary and 7.1.11 Efficacy Conclusions.

Safety:
Of the 82 subjects in the safety evaluable set, >/= grade 3:

- CRS occurred in 18%
- Neurologic toxicities occurred in 30%
- Febrile neutropenia occurred in 6%
- Prolonged cytopenias occurred in 56%, and
- Infections occurred in 32%

During ZUMA-2, life-threatening and fatal adverse reactions caused by KTE-X19 were mitigated by mandated site and investigator training, careful site selection and monitoring, instructions for early detection and management of the most serious complications, and a requirement for inpatient IP administration and inpatient monitoring for seven days following the infusion. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and neurotoxicity, and a REMS. The clinical review team determined, in consultation with OBE and CDER DRISK, that the Communication Plan as proposed by the applicant would not be sufficient. Instead, a REMS with ETASU is the appropriate approach. The foci of the REMS with ETASU are site preparation, patient education, and risk mitigation strategies, with emphasis on recognition and treatment of CRS and neurotoxicity.

Long-term safety after treatment with KTE-X19 remains a concern. Due to the lack of long-term safety data in the BLA, additional study postmarketing is warranted.

7. Integrated Overview of Efficacy

7.1 Indication #1

The efficacy analysis of KTE-X19 was based upon a single study, ZUMA-2. Please see 6 Discussion of Individual Studies/Clinical Trials for a detailed review of ZUMA-2.

7.1.9 Product-Product Interactions

Due to their immunosuppressive effect, systemic corticosteroids may impede the efficacy of KTE-X19. Prophylactic or concomitant administration of systemic corticosteroids with KTE-X19 should be avoided unless needed for treatment of CRS, neurologic toxicity, or another specific indication. During ZUMA-2, steroids were administered to 40 (59%) of the 68 Cohort 1 SAS/mITTAS subjects. Forty-eight (71%) of the 68 subjects received tocilizumab therapy. Study results should be interpreted in the context of these highly prevalent concomitant medications.

7.1.11 Efficacy Conclusions

ZUMA-2 is a Phase 2, single arm, international study which provided the data for efficacy analysis in this BLA. Patients with r/r MCL after anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a BTK inhibitor were

enrolled by undergoing leukapheresis. During product manufacturing, subjects were able to receive corticosteroid and/or BTK inhibitor bridging therapy at the discretion of the investigator. All subjects were then treated with lymphodepleting chemotherapy followed by a single infusion of KTE-X19. The pre-defined primary endpoint agreed to by FDA was ORR, as assessed by an IRRC applying the 2014 Lugano Classification criteria, among the first 60 subjects who received KTE-X19 and had the opportunity to be followed for at least six months after their first objective disease response.

As of the 24 July 2019 data cutoff, 74 subjects had been enrolled, and the planned 60 subjects had been followed for at least six months after their first objective disease response subsequent to KTE-X19 administration. Fifty-two (87%) of the 60 subjects responded, with 37 (62%) achieving CRs and 15 (25%) experiencing PRs. The median DOR could not be estimated but had a lower 95% CI bound of 358 days, with 69% of subjects censored and a median follow-up of 240 days from time of first response. Results appeared similar across subgroups and between central evaluators and site investigators.

In conjunction with the high response rates seen in the poor prognosis, r/r MCL population studied in ZUMA-2, the preliminary DOR data suggest a reasonable expectation that treatment of r/r MCL with KTE-X19 may lead to clinically meaningful efficacy. These conclusions support accelerated approval from an efficacy perspective, with longer-term follow-up data and evaluation of KTE-X19 treatment in the BTK inhibitor-naïve r/r MCL population required before a decision regarding full approval can be made.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

See 6.1.12.1 Methods.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Considering the differences in the populations of subjects studied in ZUMA-3, ZUMA-4, and ZUMA-8, the 82 subjects from ZUMA-2 compromise the safety population set and should be used as the safety population for labeling purposes. Data for ZUMA-2 included 122 subjects. Eighty-two (67%) were treated with KTE-X19, 32 (25%) did not meet screening requirements, and nine (7%) did not receive the IP.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

See 1.1 Demographic Information: Subgroup Demographics and Analysis Summary and 6.1.12.1 Methods.

8.2.3 Categorization of Adverse Events

See 6.1.12.2 Overview of Adverse Events.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

There were no pooled data. See 8.2.1 Studies/Clinical Trials Used to Evaluate Safety.

8.4 Safety Results

8.4.1 Deaths

See 6.1.12.3 Deaths.

8.4.2 Nonfatal Serious Adverse Events

See 8.4.4 Common Adverse Events.

8.4.3 Study Dropouts/Discontinuations

In the 120-Day safety update, approximately five months of additional follow-up was reported. The safety profile of KTE-X19 remained consistent with that observed at the time of the initial analysis.

8.4.4 Common Adverse Events

The small sample sizes in the current analyses precluded definitive conclusions regarding rates for adverse events. Nonetheless, the incidences of SAEs, grade >/= 3 AEs, CRS, neurologic events, and infections are similar across CAR T products.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

None.

8.5.2 Time Dependency for Adverse Events

See 6.1.12.5 Adverse Events of Special Interest (AESI).

8.5.3 Product-Demographic Interactions

See 6.1.12.1 Methods. No carcinogenicity or genotoxicity studies have been conducted with KTE-X19. The immunogenicity of KTE-X19 was evaluated using a traditional enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. A confirmatory assay demonstrated that none of the subjects treated developed antibodies after infusion.

8.6 Safety Conclusions

The safety data from ZUMA-2 demonstrate that KTE-X19 has a favorable safety profile for the intended population and was well-tolerated in the trial with a manageable adverse event profile. However, the safety profile for KTE-X19 warrants a REMS with ETASU, and because there are additional long-term safety concerns due to the use of the retroviral vector. The applicant will have to comply with an observational PMR study for short- and long-term toxicity.

In general, the safety data from ZUMA-2 are consistent with the key adverse events noted with the applicant's prior approved product, YESCARTA©.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No animal studies of reproduction or developmental toxicity have been performed, and KTE-X19 has not been studied in pregnant women.

Clinical reviewer comment
For information regarding the need for contraceptive use among patients treated with cyclophosphamide and fludarabine lymphodepleting conditioning chemotherapy, please see the respective agents' prescribing information.

9.1.2 Use During Lactation

There are no data on use of KTE-X19 during lactation.

9.1.3 Pediatric Use and PREA Considerations

There are no pediatric data in the intended population. The application does not trigger PREA, as brexucabtagene autoleucel is a new molecular entity (NME) with orphan designation.

9.1.5 Geriatric Use

Please see 6.1.11.3 Subpopulation Analyses for details.

Clinical reviewer comment
Although efficacy appears similar across subject ages in the available clinical data, there are too few subjects to adequately support any conclusions drawn from evaluations of efficacy among subjects less than 65 years old compared to those among subjects 65 years of age or older.

10. Conclusions

Efficacy

As summarized in 7.1.11 Efficacy Conclusions, the combination observed in ZUMA-2 of high ORR and CR rates with a median DOR not yet reached after all subjects in the efficacy-evaluable population with r/r MCL were followed for a minimum of six months after first objective response provides evidence of a reasonable likelihood of clinical benefit adequate to support accelerated approval of KTE-X19.

Safety

Severe CRS and neurotoxicity associated with KTE-X19 therapy are serious and life-threatening and require supportive measures. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. In addition, there is the potential for insertional mutagenesis and resultant secondary malignancies. To enhance safety, the following measures should be followed:

1. The product label will allow for a boxed warning, and the warnings and precautions will convey a treatment algorithm for CRS
2. REMS with ETASU to assure the safe use of KTE-X19
3. PMR study that is a requirement to follow recipients of the commercial product for short- and long -term toxicity

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

The following table summarizes the risk-benefit considerations for brexucabtagene autoleucel for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

Table 57. Risk-benefit analysis summary for KTE-X19.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Mantle cell lymphoma (MCL) is an aggressive B cell malignancy • MCL makes up 6% of non-Hodgkin lymphomas; incidence is 1-2 per 100,000, 3:1 M:F • Initial response rates to treatment are high, but relapse is common • Relapsed or refractory (r/r) disease is almost always ultimately fatal	• R/r MCL is a serious condition with a poor prognosis and tendency to relapse
Unmet Medical Need	• There is no clearly established standard of care for treatment of r/r MCL • Some patients cannot tolerate available salvage therapies due to age or comorbidities • The most recently approved r/r MCL therapies are BTK inhibitors, which are in confirmatory studies under accelerated approval and require daily therapy until treatment failure	• Safe, effective salvage treatments are needed for r/r MCL • Patients may benefit from single-dose treatment options

Clinical Benefit	• ZUMA-2 is a single arm, multicenter study of KTE-X19 for the treatment of adults with r/r MCL who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a BTK inhibitor
	• Lymphodepleting chemotherapy was followed by a single infusion of KTE-X19
	• The primary endpoint was ORR per IRRC in the first 60 subjects with at least six months' follow-up after their first objective disease response
	• Key efficacy results were:
	  • ORR 87% (95% CI 75.4 – 94.1)
	  • CR rate 62% (95% CI 48.2 – 73.9)
	  • Median time to response 28 days (range 24 – 92)
	• Median DOR not estimable, lower 95% CI bound 358 days
		• Based on ORR, CR rate, and preliminary DOR data, KTE-X19 has clinically meaningful activity in r/r MCL after anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a BTK inhibitor

Risk	• Major AEs associated with KTE-X19 were cytokine release syndrome (CRS), neurologic toxicities, prolonged cytopenias, infectious complications, cardiac events, and hypogammaglobulinemia	• All the evidence indicates that the risk of KTE-X19, while substantial, does not outweigh the benefit to adult patients with r/r MCL
Risk Management	• The most substantial risks of brexucabtagene autoleucel are CRS and neurologic toxicity, which were mitigated in the trial by careful site selection and training of investigators • There are theoretical risks of secondary malignancy in this genetically modified immunotherapy based on the potential for replication competent retrovirus and insertional mutagenesis	• The risks associated with KTE-X19 warrant boxed warnings, a REMS with ETASU, and a long-term follow-up study • The registry postmarketing study will follow 500 recipients of the commercial product for 15 years for secondary malignancy and short-term AEs

11.2 Risk-Benefit Summary and Assessment

The risks of brexucabtagene autoleucel are associated with its mechanism of action. CRS and neurotoxicity can be life-threatening or fatal. Hypogammaglobulinemia can persist for months and requires monitoring and intervention. However, the risks may be managed with appropriate risk mitigation strategies in place. Objective and complete response rates observed during ZUMA-2 show KTE-X19 to be an efficacious agent in the treatment of relapsed or refractory mantle cell lymphoma after prior therapies including anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a BTK inhibitor. Preliminary duration of response data suggest KTE-X19 may provide persistent benefit, although longer-term follow-up is needed to adequately evaluate this possibility. In addition, KTE-X19 represents a fundamentally different treatment modality than that of BTK inhibitors, and patients and clinicians may benefit from the ability to select one therapy type over the other. Overall, KTE-X19 has a favorable risk-benefit profile for the treatment of r/r MCL.

11.3 Discussion of Regulatory Options

Safety

The safety profile of KTE-X19 warrants a REMS with ETASU. In the IND phase, the applicant selected sites for expertise, conducted site training, and had close medical monitoring to assure that the unique adverse events were treated appropriately and that patients and medical staff were educated on the risks, particularly of CRS and neurotoxicity. There are additional long-term safety concerns due to the use of a retroviral vector. We have asked the applicant to comply with a PMR study for short- and long-term toxicity with an observational focus. Additionally, the label will be inclusive of the risks and will include risk mitigation strategies for CRS and neurotoxicity, including a requirement to monitor patients at the certified healthcare facility daily for at least seven days following infusion of KTE-X19.

Efficacy

Three regulatory options exist: regular approval, accelerated approval, and denial of approval. Approval requires substantial evidence of effectiveness, with accelerated approval accepting demonstration of a positive effect on a surrogate or intermediate endpoint reasonably likely to predict clinical benefit. Denial of approval results when a product fails to fulfill criteria for either type of approval. Key elements of effectiveness or clinical benefit are magnitude and persistence of response. The submitted ZUMA-2 data demonstrated a significant degree of efficacy by objective and complete response rates after treatment with KTE-X19 in an adequate number of subjects with mantle cell lymphoma who were relapsed or refractory to BTK inhibitors after treatment with an anthracycline- or bendamustine-containing regimen and anti-CD20 therapy, which is a group with an unmet medical need for safe, effective therapies. Duration of response data based on six months of follow-up after first response suggest the possibility of a meaningful benefit.

11.4 Recommendations on Regulatory Actions

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

Although the enrolled population in ZUMA-2 was made up of patients with disease which had relapsed after or was refractory to BTK inhibitors as well as an anthracycline or bendamustine and anti-CD20 therapy, the indication in the label is consistent with the applicant's proposed indication and represents FDA's assessment of the known and predicted treatment effects of brexucabtagene autoleucel in a more generalized population of adult patients with relapsed or refractory MCL. The clinical review team recommends consideration of the broader population based on the following reasons supporting extrapolation of the efficacy conclusions from the BTK inhibitor-exposed r/r MCL population to the generalized r/r MCL population:

1) BTK inhibitors are currently under accelerated approval to address the unmet medical need of patients with r/r MCL, and there are no FDA-approved therapies of any type for patients with MCL which is r/r to BTK inhibitors. Thus, KTE-X19 was evaluated in poor-prognosis patients with advanced disease who do not have any FDA-approved therapies available. The ZUMA-2 population was exposed to a median of three (maximum of five) prior lines of therapy, including 43% who had received an autologous hematopoietic stem cell transplant, 72% who had received anthracyclines, and 54% who had received bendamustine. The observed ORR of 87%, CR rate of 62%, and not estimable median duration of response after a median follow-up of 240 days from time of first response represent robust results in this population.
2) The clinical review team examined the ZUMA-2 population for patients who had minimal or limited exposure to BTK inhibitors to understand the nature of response to therapy with brexucabtagene autoleucel following limited or no exposure to BTK inhibitors. The sample size was limited to one subject, and therefore no meaningful conclusions could be drawn. However, the review team believes there is no mechanistic reason to predict that BTK inhibitor-naïve patients with r/r MCL would experience fewer or less durable responses to treatment with KTE-X19 than BTK inhibitor-exposed patients with r/r MCL. Additionally, analysis of the ZUMA-2 data by number of prior therapies revealed no notable differences in efficacy of treatment between subgroups. Therefore, the efficacy data from patients with r/r MCL after BTK inhibitor exposure and prior exposure to anthracycline or bendamustine therapy and anti-CD 20 treatment is sufficient to extrapolate to a population that does not necessarily have prior exposure to BTK inhibitors.

KTE-X19's efficacy in the BTK inhibitor-naïve population needs to be confirmed before regular approval can be justified. As such, the review team recommends accelerated approval of the broad indication for r/r MCL with two efficacy-related postmarketing requirements (PMRs). The first PMR study should evaluate KTE-X19 treatment of BTK inhibitor-naïve subjects, with follow-up for a minimum 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 results observed with agents currently under accelerated approval for this population. Given the single arm design necessary for the first PMR study to be completed within a reasonable timeframe, a second PMR study should provide supporting evidence of durability of response. This can be accomplished through additional follow-up of the subjects already

treated in ZUMA-2 to a minimum of 18 months from time of first objective response. In this instance, the ORR and durability of response observed thus far in ZUMA-2 is considered an intermediate clinical benefit endpoint to support accelerated approval in r/r MCL, while ORR, CR rate, and durability of response of sufficient magnitude following a minimum duration of follow-up of 18 months from time of first response in BTK inhibitor-naïve patients with r/r MCL are together considered a clinical benefit endpoint. The clinical review team also 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 in ZUMA-2. However, because this narrower population is encompassed within the broader r/r MCL population recommended for accelerated approval, the clinical review team considered a separate approval unnecessary.

Finally, the clinical team recommends including the durability of response observed to date in the product label as a component of the basis for accelerated approval. This is a departure from the labeling for other products under accelerated approval for r/r MCL. However, in the context of current standard medical care of this population, the ORR and CR rate seen in ZUMA-2 would likely have been insufficient to support accelerated approval for r/r MCL in the absence of any durability of response data. Although efficacy in BTK inhibitor-naïve patients and overall durability of response need to be confirmed in order to consider traditional approval of KTE-X19 for r/r MCL as described above, the preliminary durability of response data currently available were key to supporting the recommendation for accelerated approval. As such, it is appropriate to note in the label.

11.5 Labeling Review and Recommendations

Safety

- Inclusion of all 82 patients who received treatment in the safety population
- Modification to the warnings and precautions section to include details regarding CRS, neurologic toxicity, serious infections, prolonged cytopenias, hypogammaglobulinemia, and secondary malignancies
- Section 5.3 to describe the REMS

Efficacy

- Addition of language describing accelerated approval
- Removal of the word “target” from dosing information to specify a single approved dose
- Revision of the clinical studies section to:
    - Clarify details including the study population under consideration, subject disposition, type of bridging therapy received, and variations in study treatment administration
    - Remove information that was not clinically meaningful

11.6 Recommendations on Postmarketing Actions

Safety

The applicant is planning to conduct a postmarketing registry study which we will consider a PMR. This study is observational and focuses on short-term toxicity,

documenting adverse events, and long-term follow-up for evaluation of secondary malignancies. No routine study for RCR is planned. The plan is to enroll approximately 500 patients and follow each patient for 15 years.

Efficacy

The clinical team recommends accelerated approval of KTE-X19 for the treatment of relapsed or refractory mantle cell lymphoma (r/r MCL). Additional data in two areas are needed to confirm clinical benefit for consideration of conversion to regular approval: duration of follow-up to assess durability of response, and treatment of subjects with r/r MCL but without prior BTK inhibitor exposure to assess efficacy in this population. We recommend two PMRs, outlined below, to address these needs.

1. 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: The 18 month minimum threshold was set because therapies currently available to patients with r/r MCL, including patients who have received more than two prior treatments, have demonstrated this duration of response [see 1 Executive Summary and Table 1 in 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)]. Data will continue to be collected from ZUMA-2 Cohort 1 subjects according to the protocol's established schedule of assessments (see Tables 4 and 5 in 6.1.7 Surveillance/Monitoring) until all 60 subjects in the inferential analysis set have had the opportunity for at least 24 months' follow-up from their time of first response and the remaining eight treated subjects in Cohort 1 have had the opportunity for at least 18 months' follow-up from their time of first response. Milestone dates for this PMR are:
    - Final protocol submission: Completed; most recent protocol amendment submitted 13 November 2018
    - Study completion: 31 December 2020
    - Final study report submission: 31 July 2021

2. Study of KTE-X19 treatment of subjects with r/r MCL who have not been exposed to a BTK inhibitor: Consistent with ZUMA-2's eligibility criteria, all subjects enrolled in ZUMA-2 had previously been treated with either ibrutinib or acalabrutinib. Data from r/r MCL patients without BTK inhibitor exposure are necessary to consider conversion to regular approval of KTE-X19 for the broad indication of r/r MCL. The applicant has proposed a single arm study of 86 BTK inhibitor-naïve subjects with r/r MCL, which would account for a 10% drop-out rate while providing 90% power to detect a difference between an ORR of 75% after treatment with KTE-X19 and an historical ORR of 57%. Meta-analysis of the literature provided the historical ORR. The primary endpoint is ORR by Lugano 2014 disease response criteria as determined by an independent review committee. 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. These key study design elements are acceptable, and details of the full protocol will be finalized prior to implementation. Milestone dates for this PMR are:
    - Final protocol submission: 15 January 2021
    - Study completion: 30 April 2025
    - Final study report submission: 31 October 2025

APPENDIX A

FDA's grouped preferred terms used during analysis and in the prescribing information.

Grouped Term	Preferred Terms
Abdominal pain	Abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
Aphasia	Aphasia, dysphasia, dysarthria, communication disorder
Arrhythmia	Arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, bundle branch block right, electrocardiogram QT prolonged, extra-systoles, heart rate irregular, supraventricular extra-systoles, supraventricular tachycardia, ventricular arrhythmia, ventricular tachycardia, ventricular fib, bradycardia, sinus bradycardia
Ataxia	Ataxia, coordination abnormal, gait disturbance, balance disorder
Bacteremia (except fungal)	Staphylococcal bacteremia, enterococcal bacteremia, streptococcal bacteremia
Bacterial infection	Bacterial infection, enterococcal infection, helicobacter infection, klebsiella infection, wound infection staphylococcal, wound infection bacterial, wound infection, infected bite, tooth infection, tooth abscess, clostridium difficile infection
Cardiac failure	Acute left ventricular failure, cardiac failure, ejection fraction decreased, cardiac flutter
Coagulopathy	Coagulopathy, disseminated intravascular coagulation, INR (international normalized ratio) increased
Cough	Cough, productive cough, upper-airway cough syndrome
Cytokine release syndrome	Capillary leak syndrome, cytokine release syndrome, CRS
Cytomegalovirus infection	Cytomegalovirus enteritis, cytomegalovirus infection, cytomegalovirus viremia
Delirium	Agitation, delirium, delusion, disorientation, hallucination, restlessness, irritability, personality change, hypomania
Depression	Depression
Device related infection	Device related infection, device related sepsis, catheter infection
Diarrhea	Diarrhoea, colitis, enterocolitis
Dizziness	Dizziness, presyncope, syncope
Dyspnea	Acute respiratory failure, dyspnoea, orthopnea, respiratory distress, dyspnea
Dysgeusia	Dysgeusia
Ecchymosis	Ecchymosis, increased tendency to bruise
Edema	Face oedema, generalized oedema, local swelling, localized oedema, oedema, oedema genital, oedema peripheral, periorbital oedema, eyelid oedema, peripheral swelling, scrotal oedema, swelling face.
Encephalopathy	Cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, drowsiness, stupor, lethargy, amnesia, altered state of consciousness

Grouped Term	Preferred Terms
Enteritis	Enteritis
Fatigue	Fatigue, malaise, asthenia
Fluid overload	Fluid overload, hypervolemia
Headache	Headache, head discomfort, sinus headache, procedural headache, migraine
Herpes	Herpes simplex, herpes zoster, herpes zoster oticus, human herpesvirus 6 infection, oral herpes
Hyperbilirubinemia	Blood bilirubin increased, hyperbilirubinemia
Hypertransaminasemia	Alanine aminotransferase, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased
Hyperuricemia	Blood uric acid increased, hyperuricemia
Hypoalbuminemia	Blood albumin decreased, hypoalbuminemia
Hypomagnesemia	Blood magnesium decreased, hypomagnesemia
Hypotension	Diastolic hypotension, hypotension, orthostatic hypotension
Hypoxia	Hypoxia, oxygen saturation decreased
Immunoglobulins decreased	Blood immunoglobulin decreased, blood immunoglobulin G decreased, hypogammaglobinemia
Leukopenia	Leukopenia, white blood cell count decreased
Pneumonia	Lung infection, pneumonia, pneumonia klebsiella, pneumonia staphylococcal, lung infiltration
Lymphocytosis	Lymphocyte count increased, lymphocytosis
Lymphopenia	Lymphopenia, lymphocyte count decreased
Motor dysfunction	Muscle spasms, muscular weakness, dyskinesia, eyelid ptosis, muscle twitching, intensive care acquired weakness, mobility decreased
Musculoskeletal pain	Musculoskeletal pain, arthralgia, back pain, bone pain, flank pain, groin pain, myalgia, neck pain, pain in extremity, myalgia
Neuropathy	Neuropathy peripheral, paresthesia, paraesthesia oral, dysesthesia, allodynia, hyperalgesia, hyperaesthesia, peripheral sensory neuropathy, sciatica, nerve injury
Neutropenia	Febrile neutropenia, neutropenia, neutrophil count decreased
Oral pain	Oral pain, gingival pain, lip pain, oral mucosal erythema, oropharyngeal pain
Pain	Pain, ear pain, facial pain, non-cardiac chest pain
Pulmonary edema	Pulmonary congestion, pulmonary oedema, re-expansion pulmonary oedema
Rash	Erythema, papule, rash, rash erythematous, rash maculopapular, pustular rash, folliculitis
Renal insufficiency	Acute kidney injury, blood creatinine increased, renal impairment
Sepsis	Sepsis, septic shock
Stomatitis	Stomatitis, stomatitis necrotizing
Upper respiratory tract infection	Respiratory tract infection viral, upper respiratory tract infection, rhinovirus infection

Grouped Term	Preferred Terms
Tachycardia	Sinus tachycardia, tachycardia
Tachypnea	Respiratory rate increased, tachypnea
Thrombocytopenia	Platelet count decreased, thrombocytopenia
Thrombosis	Deep vein thrombosis, embolism, embolism venous, pulmonary embolism, splenic infarction, splenic vein thrombosis, subclavian vein thrombosis, thrombosis, thrombosis in device
Tremor	Head titubation, tremor
Urinary tract infection	Urinary tract infection, urosepsis
Upper respiratory infection	Respiratory tract infection viral, upper respiratory infection, rhinovirus infection
Viral infection	Metapneumovirus infection, respiratory syncytial virus infection, parvovirus infection, enterovirus infection, parainfluenza virus infection
Weight decreased	Abnormal loss of weight, weight decreased

Megan Zimmerman, MD

Helkha Peredo Pinto, MD MPH

Margret Merino, MD

Bindu George, MD

Marc Theoret, MD