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BLA Clinical Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplemental BLA
Application Number(s)	125703/91
Priority or Standard	Priority
Submit Date(s)	01 April 2021
Received Date(s)	01 April 2021
PDUFA Goal Date	01 October 2021
Division/Office	DCEPT/OTAT
Review Completion Date	01 October 2021
Established Name	Tecartus
(Proposed) Trade Name	KTE-X19 (brexucabtagene autoleucel)
Pharmacologic Class	CD19-directed, genetically-modified autologous T cell immunotherapy
Applicant	Kite Pharma, Inc.
Formulation(s)	Cryopreserved injection containing genetically modified autologous T cells in CryoStor (dimethyl sulfoxide [DMSO], final concentration, 5%), sodium chloride (NaCl), and human serum albumin (HSA), and supplied in a patient-specific infusion bag containing approximately 68 mL
Route(s) of Administration	Intravenous (IV)
Dosing Regimen	Single dose with a target of 1 x 10^6 CAR-positive T cells/kg (maximum 2 x 10^8 cells) administered by 30-minute IV infusion, and preceded by fludarabine and cyclophosphamide conditioning chemotherapy
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (B-ALL)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (pre-B ALL)
Orphan Drug Designation	Yes

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Reviewers of the BLA Clinical Review and Evaluation

Reviewers of Application

Clinical Reviewer	Najat Bouchkouj, MD
OCE Clinical Team Leader	Donna Przepiorka, MD, PhD
Branch Chief (CHB)	Bindu George, MD
OCE Director (or designated signatory authority)	Marc Theoret, MD
Division Director (DCEPT)	Tejashri Purohit-Sheth, MD

CHB: Clinical Hematology Branch
DCEPT: Division of Clinical Evaluation and Pharmacology/Toxicology
OCE: Oncology Center of Excellence

Glossary

ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALL	acute lymphoblastic leukemia
Allo SCT	allogeneic stem cell transplant
AR	adverse reaction
AUC_{0-28}	area-under-the-curve from Day 0 to Day 28
B-ALL	B-cell precursor acute lymphoblastic leukemia
BLA	Biologics License Application
CAR	chimeric antigen receptor
CC	conditioning chemotherapy
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing and controls
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
GT	grouped terms
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free suvival
DOR	duration of remission
ECG	electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
ETASU	elements to assure safe use
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	graft-versus-host disease
HLH/MAS	hemophagocytic lymphohistiocytosis/macrophage activation syndrome
ICH	International Council for Harmonisation
IPD	important protocol deviation
ISS	integrated summary of safety

IR	information request
KM	Kaplan-Meier
KTE-X19	brexucabtagene autoleucel, TECARTUS®
LD	lymphodepletion
MCL	mantle cell lymphoma
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRD	minimal residual disease
NE	not evaluable, not estimable
NT	neurologic toxicity
(b) (4)	
OCR	overall complete remission
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
Ph	Philadelphia chromosome
Pre-B ALL	B-cell precursor acute lymphoblastic leukemia
R/R	relapsed/refractory
RCR	replication-competent retrovirus
RFS	relapse-free survival
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SCT	stem-cell transplant
SOC	system organ class
SPOOS	significant payments of other sorts
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
US	United States
VAS	visual analogue scale
VIS	vector integration site

1 Executive Summary

1.1. Product Introduction

FDA Assessment:

Brexucabtagene autoleucel (KTE-X19) is an engineered autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the US and European Union (EU) for the treatment of adult patients with relapsed/refractory (r/r) mantle cell lymphoma (MCL) under the tradename Tecartus®.

KTE-X19 is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell product engineered to recognize the transmembrane glycoprotein CD19. It comprises autologous peripheral-blood T cells that are selected with (b) (4) and transduced with a murine retroviral vector expressing an anti-CD19 CD28/CD3ζ CAR. When KTE-X19 engages CD19-positive targets, the modified T cells receive signals to activate and proliferate 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 pre-B ALL.

The Applicant is developing KTE-X19 for the treatment of adult patients with r/r B-cell precursor acute lymphoblastic leukemia (pre-B ALL). These patients have poor outcomes and represent a population with an unmet medical need that warrants novel treatment strategies.

1.2. Conclusions on the Substantial Evidence of Effectiveness

FDA Assessment:

The review team recommends regular approval of brexucabtagene autoleucel (KTE-X19) for the treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (pre-B ALL). This is an extension of the existing indication in adult patients with r/r mantle cell lymphoma (MCL), which received accelerated approval in July 2020. The recommended dose for the r/r pre-B ALL indications is a target of 1×10^6 CAR-positive T cells/kg (maximum 1×10^8 cells) administered by 30-minute intravenous infusion and preceded by fludarabine and cyclophosphamide for lymphodepletion.

In support of the Applicant's proposed indication, the Applicant submitted safety and efficacy data from the clinical study, ZUMA-3, as well as supplemental safety data from three other studies (ZUMA-4, ZUMA-8, and ZUMA-18).

Efficacy and safety are based on a single arm, Phase 1/2, multicenter study (ZUMA-3) that evaluated a single infusion of KTE-X19, preceded by lymphodepleting chemotherapy, for the treatment of subjects with r/r pre-B ALL. Subjects were enrolled by undergoing leukapheresis. During product manufacturing, subjects were to receive bridging therapy at the discretion of the investigator. Per protocol, the primary endpoint is the overall complete response (OCR) rate defined as the combined rate of complete response (CR) and CR with incomplete hematological recovery (CRi) per central assessment in the modified intent-to-treat (mITT) analysis set. Key secondary endpoints included duration of response (DOR), OCR by investigator assessment and minimal residual disease (MRD).

In total, 71 subjects were enrolled (i.e., underwent leukapheresis), and 55 subjects received KTE-X19, 54 of whom constituted the primary efficacy analysis set. Among the 54 subjects in the primary efficacy analysis set, 25 (46%) had refractory relapse, 14 (26%) had primary refractory disease, 11 (20%) had untreated second or later relapse, and 4 (7%) had untreated early first relapse. Seventy-eight (78) subjects were included in the safety analysis set which comprised data from all subjects in the Phase 2 cohort in addition to subjects from the Phase 1 who received KTE-X19 at a dose of 1×10^6 anti-CD19 CAR T cells/kg, which is the intended dose for approval.

Efficacy

The prespecified primary endpoint for the Phase 2 pivotal cohort, as defined by the Applicant, was OCR; however, FDA considers CR rate as the optimal primary endpoint to inform a regulatory decision for regular approval. Moreover, FDA considers a CR within 3 months from start of therapy to reflect a clinical benefit for patients with r/r pre-B ALL treated with CAR T-cell therapies. FDA has considered using durable CR for determination of clinical benefit on the basis of recovery of adequate blood counts to protect against infection and avoidance of transfusions.

As of the 9 September 2020 cutoff, 71 subjects were enrolled in the Phase 2 cohort, 55 were treated with KTE-X19 and 54 subjects met criteria to be included in the primary efficacy analysis. One subject was excluded because of lack of disease post-bridging chemotherapy. Among the 16 subjects who did not receive KTE-X19, seven subjects didn't receive it due to adverse events (AEs) (two of whom had manufacturing failure), three subjects no longer met eligibility criteria, and four subjects due to manufacturing failure (for a total manufacturing failure of 8%).

A total of 35 subjects (65%) (95% exact Clopper-Pearson confidence interval [CI]: 51, 77) in the primary efficacy population (n=54) had a best overall disease response of CR or CRi, as determined by central assessment. As a result, the lower limit of the 95% CI for OCR is 51%, which is above the preset null hypothesis rate of 40%. CR rate was 54% (95% CI 40, 67) with a

median DOR that was not reached after a median follow-up from time of first response of 5 months (0.03+, 16.07+). CR rate within 3 months of infusion of KTE-X19 was 52% (95% CI 38, 66). The duration of CR was estimated to exceed 12 months for more than half the subjects. Among all 71 enrolled (i.e., leukapheresed) subjects, OCR was observed in 36 subjects (51%) (95% CI 39, 63) and CR rate in 30 subjects (42%) (95% CI 31, 55).

The magnitude of the treatment effect was consistent across the subpopulation analyses in relation to key disease or treatment characteristics. This is concluded to be substantial evidence of the effectiveness of KTE-X19 for treatment of adult subjects with relapsed or refractory pre-B ALL.

The overall results of a high CR with durable response in a heavily pretreated population of adults with r/r ALL, even with a small sample size justifies a regular approval for KTE-K19. These results with a single agent indicate that the targeted KTE-X19 not only acutely treats the r/r pre-B ALL but has persistence that allows for a durable response unlike that seen with multiagent therapy or hematopoietic stem cell transplant (HSCT) in a comparable historical population.

Safety

The safety analysis set included all 78 subjects from ZUMA-3 Phase 2 and Phase 1 cohort who were treated with one dose of KTE-X19 at 1 x 10^6 cells/kg. The most common non-laboratory adverse reactions (incidence ≥ 20%) included fever, cytokine release syndrome (CRS), hypotension, encephalopathy, tachycardia, nausea, chills, headache, fatigue, febrile neutropenia, diarrhea, musculoskeletal pain, hypoxia, rash, edema, tremor, infection with pathogen unspecified, constipation, decreased appetite, and vomiting. The most comment Grade 3 or 4 laboratory abnormalities included: leukopenia (99%), neutropenia (97%), lymphopenia (96%), thrombocytopenia (87%), anemia (77%), hypophosphatemia (47%), increased alanine aminotransferase (31%), increased aspartate aminotransferase (23%), hyperglycemia (22%) and hypocalcemia (22%).

Serious adverse events (SAEs) occurred in 62 (79%) subjects and included CRS, febrile neutropenia, hypotension, encephalopathy, fever, Infections with pathogen unspecified, hypoxia, tachycardia, bacterial infection, respiratory failure, seizure, diarrhea, dyspnea, fungal infection, viral infection, coagulopathy, delirium, fatigue, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), musculoskeletal pain, edema, and paraparesis. SAEs Grade 3 or higher occurred in 54 (37%) subjects and included hypotension, encephalopathy, fever, Infections with pathogen unspecified, hypoxia, tachycardia, bacterial infection, respiratory failure, seizure, diarrhea, dyspnea, fungal infection, viral infection, coagulopathy, delirium, fatigue, HLH/MAS, musculoskeletal pain, edema, and paraparesis. Grade 3 or higher adverse reactions occurred in 76 (97%) subjects. Four subjects had fatal adverse reactions: one with cerebral edema and three with infections (sepsis and

fungal pneumonia). Three subjects had ongoing CRS events at the time of death, one of whom had fatal cerebral edema.

Any grade of CRS occurred in 72 (92%) subjects, and neurologic toxicity occurred in 68 (87%) subjects. Most common Grade 3 or higher adverse events of special interest (AESI) included: prolonged cytopenias (47 subjects; 61%), febrile neutropenia (27 subjects; 35%), neurologic toxicities (NT) (27 subjects; 35%), infections (23 subjects; 30%), and CRS (20 subjects; 26%).

Among the 35 responders in the primary efficacy analysis set, four subjects (11%) had Grade 3 or higher prolonged cytopenia that didn't resolve by Day 60 and included neutropenia in 3 (9%) subjects and thrombocytopenia in two (6%) subjects.

During conduct of the ZUMA-3 study, risk of life-threatening and fatal adverse reactions attributed to KTE-X19 was 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 CRS and NT, and a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU). The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies with emphasis on early recognition and treatment of CRS and NT. To alert prescribers to clinically significant, serious, life-threating and fatal adverse reactions associated with KTE-X19, the following events will be included in the Warning and Precautions section of the label: CRS, NT, serious infections, prolonged cytopenias, hypogammaglobulinemia, and secondary malignancies. Life-threatening HLH/MAS was identified as a new safety signal in this application whereas it did not occur in subjects with MCL. Therefore HLH/MAS will be added in the Warning and Precautions section of the label. Because the most common AESIs were similar between Studies ZUMA-3 and ZUMA-2 (the study that was the basis for approval of KTE-X19 in r/r MCL), the incidence of the most common AESIs will be presented, in the label, combined for both studies except when discussing details of CRS and NT due to difference in incidence and timing of onset of these events in the two patient population.

Overall, no new safety signals were identified in this submission except for HLH/MAS, which is a known adverse reaction that has been associated with the same class of drug products. CRS and NT associated with KTE-X19 therapy are serious, life-threatening and can be fatal. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. Because of the observed delayed onset of NT and CRS events beyond the first 7 days following KTE-X19 infusion, the recommended daily monitoring for these symptoms will be revised from 7 days to 14 days to allow for closer monitoring. The theoretical concerns include an increased risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional mutagenesis. There were no events of RCR infection or

insertional mutagenesis reported in the sBLA. None of the secondary malignancies during this study were attributed to the study product. Due to the lack of long-term safety data in the sBLA, a postmarketing requirement (PMR) long-term follow-up registry study will be required to follow recipients of the commercial product for short term and long-term toxicity up to 15 years.

In summary, Study ZUMA-3 represents an adequate and well-controlled study that provides substantial evidence of effectiveness based on complete response rate and durability of response in subjects with r/r pre-B ALL in the context of an acceptable safety profile in support of regular approval. Given the life-threatening nature of the disease in the indicated population, the adverse reactions of CRS and NT, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective in the intended population. Thus, the overall benefit-risk profile favors regular approval of KTE-X19 in adult patients with r/r pre-B ALL.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The table below summarizes the benefit-risk considerations for KTE-X19 for the treatment of adult patients with r/r pre-B ALL.

The overall results of a high response rate coupled with durable response in a heavily pretreated population of adults with r/r ALL, indicate a robust evidence of effectiveness of KTE-X19. In addition, KTE-X19 represents a fundamentally different treatment modality than that of other therapies available for the intended population.

Overall, except for HLH/MAS, no other new safety signals were identified. The risks of KTE-X19 are associated with its mechanism of action. CRS and NT can be life-threatening or fatal. Hypogammaglobulinemia may predispose patients to infections and requires monitoring and intervention. However, these risks may be managed with the mitigation strategies in place. Therefore, these toxicities represent toxicities that are acceptable from a benefit-risk perspective in the intended population. Thus, the overall benefit-risk profile favors regular approval of KTE-X19 in adult patients with r/r pre-B ALL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with R/R ALL do not survive without treatment. • Long-term survival is <1% for patients with relapsed or refractory B-cell ALL (R/R ALL). • 5-year OS rates for adults is low at approximately 20% to 40%	• R/R ALL is a fatal disease
Current Treatment Options	• Treatment approach includes the use of several antineoplastic agents given in varying doses and schedules, HSCT, novel therapeutic agents (e.g., blinatumomab or inotuzumab), which do not induce long-term remission and are dependent on subsequent HSCT • Remission rates using current available	• ALL after second or subsequent relapse or refractory to initial induction chemotherapy is highly resistant to salvage chemotherapy based on prior exposure to standard of care chemotherapy and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	therapy are low - <10% with single agents and 25-46% with combination chemotherapy, and . • Even with allogeneic HSCT, survival is only about 35%. • Duration of first CR, age, white blood cell count at diagnosis, refractoriness to prior therapy, number of relapses, and subsequent HSCT are known prognostic factors for survival after salvage chemotherapy	hematopoietic stem cell transplantation (HSCT) • R/R ALL has a poor prognosis with standard of care therapy including HSCT and prognosis is influenced by disease biology, patient characteristics, and prior therapy. • R/r pre-B ALL in adults represent unmet medical need • Patients may benefit from single-dose treatment options
Benefit	• ZUMA-3 was a single-arm, multisite, international study for the treatment of adult subjects with r/r pre-B ALL • Subjects were treated with one course of lymphodepleting chemotherapy followed by a single infusion of KTE-X19 • The primary endpoint by the Applicant was OCR (CR+CRi), and the objective was to demonstrate an OCR that excluded 40%; while the primary evidence of effectiveness by FDA was based on CR rate. • In the Efficacy Analysis Set (N=54), the OCR was 65% (95% CI 51, 77). The CR rate was 54% (95% CI 40, 67) with a median follow-up of 5 months (0.03+, 16.07+), the median duration of remission was not reached. • CR rate within 3 months of infusion of KTE-X19 was 52% (95% CI 38, 66).	• The evidence for clinical benefit for r/r pre-B ALL in adults is compelling based on CR rate and DOR
Risk and Risk Management	• The most substantial risks of KTE-X19 were CRS, NT, HLH/MAS, prolonged cytopenias, serious infections, and persistence of hypogammaglobulinemia	• The evidence indicates that the risk of KTE-X19, while substantial, does not

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• CRS and NT were mitigated in the trial by careful site selection and training of investigators. • There are theoretical risks for second malignancy in this genetically modified immunotherapy based on the potential for replication competent retrovirus due to the lentivirus and insertional mutagenesis	outweigh the benefit in adults with r/r pre-B ALL • The risks associated with KTE-X19 warrant boxed warnings, a REMS with ETASU and a long-term follow-up study. • The PMR study will follow 500 recipients of the commercial product for 15 years for secondary malignancy and other safety signals • The OBE reviewers are working with the Applicant to finalize the YESCARTA TECARETUS REMS with ETASU major modification

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	Section 8.1.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Acute lymphoblastic leukemia (ALL) is a heterogeneous group of lymphoid disorders resulting from the clonal proliferation of immature lymphocytes of B- or T-cell lineage in the blood, bone marrow, and other organs {Terwilliger 2017}. The disease occurs with a bimodal age distribution, with 55% of cases diagnosed in patients < 20 years old and 28% of cases diagnosed in adult patients ≥ 45 years old {National Comprehensive Cancer Network 2020}. In the United States (US), approximately 6,000 new ALL cases are diagnosed per year, and approximately 1,500 deaths from ALL occur per year. While 5-year overall survival (OS) rates for children are 89%, survival rates for adults remain low at approximately 20% to 40%, and the majority of ALL deaths are in adults {Geyer 2017, National Comprehensive Cancer Network 2020, Siegel 2020}.

Approximately 25% of adult patients with ALL have Philadelphia chromosome-positive (Ph^+) disease {National Comprehensive Cancer Network 2020}, which confers a poor prognosis with 5-year OS and relapse-free survival (RFS) rates of 8% and 0%, respectively {Pullarkat 2008}. Among those with primary refractory or primary relapsed (r/r) ALL, patients with short first remissions (< 12 months) have worse outcomes than patients who relapse after a longer first remission (complete remission [CR] rates of 22% vs 41%, respectively) {Thomas 1999}. With each subsequent therapy, the prognosis gets worse. Survival rates for patients with r/r B-ALL 1 year after the second, third, and fourth or higher lines of therapy are 26%, 18%, and 15%, respectively {Gokbuget 2016b}. CR rates with second-line and higher chemotherapy are ≤ 47% vs ≤ 21% with third-line and higher chemotherapy {Advani 2010, Faderl 2011, Gokbuget 2016b, Kantarjian 2003, O'Brien 2013, Tavernier 2007, Thomas 1999}.

The FDA's Assessment:

FDA agrees with the Applicant's statement that adults with r/r ALL have an unfavorable prognosis, which is influenced by disease biology, patient characteristics, and prior therapy. Duration of first CR, age, white blood cell count at diagnosis, refractoriness to prior therapy, number of relapses, and subsequent HSCT are known prognostic factors for survival outcomes[1,2].

[1] Nicola Gökbuget, et al; International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractor y acute lymphoblastic leukemia. Haematologica 2016

[2] Gokbuget N,et al; Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood. 2012

2.2. Analysis of Current Treatment Options

Available Therapies in the r/r B-ALL Setting

Standard first-line treatment involves the use of several antineoplastic agents given in varying doses and schedules {Hoelzer 2016, National Comprehensive Cancer Network 2020}. While initial CR rates in adults are high (80% to 90%) and median duration of first remission in most studies is at least 18 months, most patients eventually relapse {Kantarjian 2004, Kantarjian 1994, Larson 1995, Rowe 2005}.

Overall, the therapeutic approaches are not strictly defined in the r/r setting but are rather based on already exhausted treatment options and the availability of remaining therapies with the intent to induce another CR. Second-line chemotherapy yields remissions in approximately 20% to 40% of patients; the remission rates are lower in patients who relapse within 12 months of an initial response {Advani 2010, Faderl 2011, Tavernier 2007, Thomas 1999}.

Disease-free survival (DFS) rates with allogeneic stem cell transplant (allo-SCT) are superior to those with chemotherapy in the salvage setting, but only 30% to 40% of patients who achieve a second CR are eligible for allo-SCT, and fewer than half are able to undergo transplant before experiencing relapse {Fullmer 2009}. As such, allo-SCT can serve as a meaningful option for patients with r/r ALL, but only a minority of patients are eligible for transplant, and few of these patients achieve a meaningful remission.

Novel therapeutic options, such as blinatumomab or inotuzumab, yield higher complete remission rates but are largely dependent on subsequent SCT and do not induce long-term remission.

The full approval of the bispecific CD19-directed CD3 T-cell engaging agent blinatumomab in the US and EU for the treatment of r/r B-ALL was based on the Phase 3, randomized, open-label, active-comparator TOWER study in subjects with Ph^{-}, r/r B-ALL {BLINCYTO 2020, Kantarjian 2017}. The study met its primary endpoint of OS comparing the blinatumomab arm with the standard-of-care chemotherapy arm (median OS of 7.7 months vs 4.0 months). Blinatumomab treatment also resulted in improved CR rates compared with chemotherapy (33.6% vs 15.7%) and combined rates of CR/CR with incomplete hematologic recovery (CRi) (35.1% vs 20.1%) {Kantarjian 2017}. Among all subjects with CR/CRi/CRh, the median duration of remission (DOR) was 7.3 months in the blinatumomab arm and 4.6 months in the chemotherapy arm. Subjects receiving blinatumomab as a second or later salvage therapy had a CR/CRi rate of 28.7%; the median OS was 5.1 months {Dombret 2019}.

A second approved novel agent is the CD22-directed antibody-drug conjugate inotuzumab ozogamicin, which was approved based on the Phase 3, randomized, open-label, multicenter INO-VATE study of subjects with $CD22^{+}$, r/r B-ALL {BESPONSA 2018}. The primary endpoints

were CR/CRi rate and OS {Kantarjian 2016}. The CR/CRi rate was significantly higher in the inotuzumab arm compared with the chemotherapy arm (80.7% vs 29.4%), with CR rates of 35.8% vs 17.4%. The minimal residual disease-negative (MRD^-) rate among subjects who achieved a CR/CRi was higher in the inotuzumab arm compared with the chemotherapy arm (78% vs 28%). In a follow-up analysis, the CR/CRi rate among treated subjects was 73.8% in the inotuzumab arm and 35.0% in the chemotherapy arm; the median DOR among subjects who achieved a CR/CRi was 5.4 months vs 4.2 months, respectively {Kantarjian 2019}. In the INO-VATE study {Kantarjian 2019}, 66% of subjects had received only 1 prior line of therapy, and the duration of the first remission had been ≥ 12 months for 43% of the subjects. This latter point is notable because a longer duration of first remission in r/r ALL is associated with improved survival outcomes after subsequent treatments {Gokbuget 2016b}.

More recently, tisagenlecleucel, an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, was approved for the treatment of r/r B-ALL in pediatric and young adult patients up to 25 years of age {Kymriah 2018a, KYMRIAH 2018b}. In the single-arm, multicenter Phase 2 ELIANA study that included subjects aged 3 to 23 years old, a CR/CRi rate of 83% was achieved {KYMRIAH 2018b}. The benefit–risk of tisagenlecleucel is not established in adult patients older than 25 years of age, and the (b) (4)

The Applicant's Position:
Despite approvals of novel therapies, median OS remains low and median DOR remains shorter than 8 months. Further, a substantial number of patients rely on subsequent allo-SCT with the risk of additional transplant-related morbidity and mortality. This highlights the need for additional therapies that can induce deeper and more durable responses in adult patients with r/r B-ALL. A second challenge is management of older patients with r/r B-ALL who often are ineligible for intensive chemotherapy regimens or allo-SCT. High risk features, such as Ph^+ status, are also increased in older patients with ALL {Gokbuget 2016a, Sawalha 2018}.
The reported results for clinical trials with inotuzumab and blinatumomab indicate that long-term remission is not achieved with these therapies in the r/r setting. A large portion of subjects treated with inotuzumab or blinatumomab still require subsequent SCT and generally experience remissions shorter than 8 months. These products also have unique considerations regarding administration and safety: blinatumomab requires continuous intravenous infusion {BLINCYTO 2020}, while inotuzumab is associated with an increased risk of veno-occlusive hepatic disease, which could interfere with the potentially curative effects of allo-SCT {BESPONSA 2018, Fan 2014}.

Thus, r/r B-ALL in adult patients continues to represent an area of great unmet medical need due to the increased relapse rate after initial therapy, worse prognosis with each subsequent relapse, and frequent ineligibility of older patients for intensive chemotherapy or SCT.

Table 1 Kite - Summary of Treatment Armamentarium (Novel Targeted Agents) Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval and Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments; adults only						
blinatumomab	r/r B-cell precursor ALL in adults	Initial Accelerated approval: 2014 Full approval: 2017	2 cycles of Blincyto for induction followed by 3 cycles for consolidation and up to 4 cycles of continued therapy	MT103-211 [NCT01466179]: single arm, open-label, multicenter study CR: 32.4% mDOR: 6.7 months MRD-ve CR/CRh: 75.3% TOWER Study [NCT02013167]: randomized, open-label, multicenter study of Blincyto compared to SOC chemotherapy CR: 34% mOS [Blin vs SOC]: 7.7 months vs 4.0 months	Cytokine Release Syndrome Neurological Toxicity [Blinatumomab Prescribing Information, Amgen]	Tower: CR 34% based on CD19 naive patient population; mOS of blinatumomab arm of 7.7 months with subsequent allogeneic SCT of 24% {Kantarjian 2017}
inotuzumab ozogamicin	r/r B-cell precursor ALL	Full approval: 2017	Dosing regimen depends on response to treatment	INO-VATE ALL [NCT01564784]: randomized, open-label, multicenter study of inotuzumab vs investigator's choice of chemotherapy. CR [Ino vs chemo]: 35.8% vs 17.4%. mDOR [Ino vs. chemo]: 8 vs 4.9. MRD-ve CR/CRi [Ino vs. chemo]: 78.4% vs 28.1%. OS: did not meet statistical significance, mOS [Ino vs chemo]: 7.7 vs 6.2 months	Hepatotoxicity, including hepatic veno-occlusive disease (VOD) Increased risk of post-hematopoietic stem cell transplant non-relapse mortality [Inotuzumab ozogamicin Prescribing Information, Pfizer]	Ino-Vate: CR 35.8% based on CD22 naive patient population; mOS 7.7 months with 24% subsequent SCT VOD in patients underwent SCT post Ino 23% vs 3% in all treated
Other Treatments; pediatric and adolescent						
Tisagenlecleucel	r/r B-cell precursor ALL**	Full approval: 2017	Based on patient weight reported at the time of leukapheresis: Patients 50 kg or less: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight. Patients above 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells	ELIANA [NCT02228096]: open-label, multicenter single-arm study CR: 63% MRD-ve CR/CRi: 83%	Cytokine Release Syndrome Neurological Toxicity [Tisagenlecleucel Prescribing Information, Novartis]	Only approved in adolescent patients <26 years; Efficacy data in the pivotal trial was in CD19 naïve patients with no prior use of blina and only 10% were primary refractory

*Accelerated approval or full approval

** Only approved for Patients up to 25 years and for r/r ALL that is refractory or in second or later relapse

The FDA's Assessment:
In addition to the Applicant's analysis of available therapies in the r/r B-ALL setting, Table 2 lists the drugs with FDA approval for r/r Philadelphia (Ph)-positive or Ph-negative precursor B-cell ALL.

Table 2 FDA - Approved Agents with Indication(s) Relevant to the Treatment of Relapsed or Refractory Precursor B-cell ALL

Agent	Excerpted Indication
Asparaginase (E. coli)	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL)
Asparaginase (Erwinia)	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E.coli-derived asparaginase
Blinatumomab	Treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children
Clofarabine*	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens
Cyclophosphamide	Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to cyclophosphamide treatment: acute lymphoblastic (stem-cell) leukemia in children
Cytarabine	Useful in the treatment of acute lymphocytic leukemia
Daunorubicin	In combination with other approved anticancer drugs is indicated for remission induction in acute lymphocytic leukemia of children and adults
Dasatinib	Treatment of adults with Ph+ ALL resistant to or intolerant of prior therapy
Dexamethasone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Doxorubicin	To produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia

Agent	Excerpted Indication
Imatinib	Treatment of adult and patients with relapsed or refractory Ph+ ALL; in combination with chemotherapy for first line treatment of pediatric patients with newly diagnosed Ph+ ALL
Inotuzumab ozogamicin	Treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Mercaptopurine	For maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen
Methotrexate	Used in maintenance therapy in combination with other chemotherapeutic agents
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Pegasparaginase	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL and hypersensitivity to native forms of L-asparaginase
Ponatinib	ALL that is Ph+ and has the T315I mutation
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Teniposide	In combination with other approved anticancer agents, is indicated for induction therapy in patients with refractory childhood acute lymphoblastic leukemia
Tisagenlecleucel	Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
Vincristine	Indicated in acute leukemia
Vincristine sulfate liposome	Treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies

Source: FDA Reviewer
*Accelerated approval only

Table 3 provides a summary of CR rates achieved with conventional combination chemotherapy or single-agent use of approved targeted therapies for adults and children with ALL[3]. Duration of first CR, age, white blood cell count at diagnosis, and number of relapses are known prognostic factors for reinduction of remission[4, 5]. Notably, the definition of CR across clinical studies is based on general clinical practice guidelines and varies across the study groups or centers.

Table 3 FDA - Summary of Treatment Armamentarium (Novel Targeted Agents) Relevant to the Proposed Indication

Agent	Population	Number of Patients	% CR (95% CI)
Clofarabine	Children	61	12% (5% - 22%)
Vincristine liposome	Adults	65	5% (1% - 13%)
Blinatumomab	Children Adults	70 185 271	17% (9% - 28%) 32% (26% - 40%) 34% (28% - 40%)
Inotuzumab ozogamicin	Adults	109	36% (27% - 46%)
Tisagenlecleucel	Children and young adults	63 [78]*	63% (50% - 75%) [51% (40% - 63%)]*
Combination chemotherapy	Children Salvage 2 Salvage ≥3	108 121	44% (35% - 54%) 19% (12% - 27%)
Combination chemotherapy	Adults Salvage 2 Salvage 3	275 125	21% (16% - 26%) 11% (6% - 18%)
Allogeneic HSCT	Adults	84	79% (68% - 87%)

Source: FDA Reviewer
*Based on 78 enrolled patients

[3] O'Leary, M et al; Approval Summary: Tisagenlecleucel for Treatment of Patients with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia. Clin Cancer Res 2019
[4] Nicola Gökbuget, et al; International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractor y acute lymphoblastic leukemia. Haematologica 2016
[5] Gokbuget N,et al; Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood. 2012

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
TECARTUS® (brexucabtagene autoleucel or KTE-X19) was initially designated as a Breakthrough Therapy for the treatment of adult patients with r/r B-cell precursor acute lymphoblastic leukemia (B-ALL) on 20 December 2017 and for the treatment of adult patients with r/r mantle cell lymphoma (MCL) on 15 June 2018. The original Biologics License Application (BLA; 125703) was granted accelerated approval on 24 July 2020 for the treatment of adult patients with r/r MCL. In addition, Kite submitted 1 labelling Prior Approval Supplement (BL 125703/0) on 25 August 2020 to update the Warnings and Precautions section; it was approved on 24 February 2021.

The FDA's Assessment:
FDA agrees. The MCL indication is the only approved indication for KTE-X19.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
Orphan Drug Designation: KTE-X19 was granted orphan drug status for the treatment of ALL (Designation No. 15-5158) on 20 April 2016.
Breakthrough Therapy Designation: KTE-X19 was granted Breakthrough Therapy Designation (BTD) on 20 December 2017 for the treatment of adult patients with r/r B-ALL.
Other Regulatory Interactions Relevant to the Proposed Application: relevant formal meetings with the FDA are summarized in m2.5, ZUMA-3 Clinical Overview, Section 1.2.4. Formal FDA responses from these meetings are provided in m1.6.3. Planned regulatory interactions, and key aspects of the registrational ZUMA-3 study and the registration package were discussed with the Agency in a Type B, Initial Multidisciplinary Breakthrough Therapy Designation Meeting. The format and content of the registration package were further discussed at a Type B meeting. A Type B pre-supplemental BLA (sBLA) teleconference discussed topline clinical data from ZUMA-3 and sought further alignment on the submission package. As part of the pre-sBLA meeting minutes, the FDA requested inclusion of this assessment aid with the sBLA submission.

The FDA's Assessment:
Development of KTE-X19 for treatment of r/r ALL was conducted under IND 16675. A summary of the regulatory actions and key interactions with FDA regarding KTE-X19 development is provided in Table 4.

Table 4 FDA - Key Regulatory Milestones for KTE-X19 Development

Date	Regulatory Activity
07 May 2015	Original protocol
20 April 2016	Orphan Drug Designation granted for treatment of acute lymphoblastic leukemia
08 August 2017	Type B End of Phase 1 (EOP1) - Design of ZUMA-3
20 December 2017	BTD for the treatment of adult patients with r/r B-ALL
15 May 2018	Type B meeting – Initial multidisciplinary BTD for KTE-X19 for r/r B-ALL - Meeting minutes
07 April 2020	Type B meeting – Format and content of planned sBLA for KTE-X19 for r/r B-ALL – Written responses
24 February 2021	Type B meeting – Pre-sBLA for KTE-X19 – Meeting minutes
01 April 2021	BLA 125703/91 Supplement received, including the Assessment Aid

Source: FDA Reviewer

The Applicant did not submit a request for Special Protocol Assessment, so there were no formal agreements on size and design of the pivotal trial. FDA provided the following key advice to the Applicant at the formal meetings:

- Recommendation to include, in the ZUMA-3 Study, a patient population that has failed multiple prior regimens to provide a greater opportunity to meet the unmet medical need for the intended patient population given the potential evolving therapeutic landscape for r/r ALL. [End of Phase 1 (EOP1)]
- KTE-X19 dose exploration should be finalized in the Phase 1 portion of the study. [EOP1]
- Subjects with negative cerebrospinal fluid (CSF) at baseline (i.e., CNS-1) are not required to undergo lumbar puncture in order to establish response posttreatment. [EOP1]
- Strongly recommending that the primary efficacy endpoint be determined by an independent review committee, and assessments of subjects who have extramedullary disease and require imaging be reviewed by an Imaging Review Charter. [EOP1]
- Plan to submit all marrow reports and other ancillary testing (e.g., CBCs, MRD assay results) to allow confirmation of response and DOR by FDA. [EOP1]
- Submit an assessment of the comparability of (b) (4) processes [EOP1]
- Hypothesis testing should primarily address CR rate in the study as CRi is not an efficacy endpoint used for regulatory decision making. Durability of response is an important supporting information in a single-arm trial. [Initial breakthrough therapy designation (BTD)]
- The plan to conduct the primary analysis when all treated subjects in Phase 2 have been evaluated for response 6 months after the KTE-C19 infusion or discontinued earlier is acceptable. [Initial BTD]

- Narratives for all treatment-emergent Grade 2 and higher CRS and neurologic events should be provided in the sBLA submission to facilitate FDA's review and adjudication of CRS and neurologic toxicity events. [Planned sBLA]
- If MRD data are proposed to be included in labeling, all assay information per the MRD guidance (including assay validation and individual test results) should be submitted. On the basis of the assay procedure described, FDA waived the need to submit the individual input quantities for each individual test result. [Planned sBLA and Pre-sBLA]
- Data from the Phase 1 portion of ZUMA-3 should also be submitted in the sBLA as supporting evidence. [Pre-sBLA]
- FDA agreed with the Applicant's plan to submit the REMS document and materials no later than 30 days after the sBLA submission. [Pre-sBLA]

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Compliance and Biologics Quality (OCBQ)

Not applicable for this supplement.

4.2. Product Quality

The FDA's Assessment:

TECARTUS® (brexucabtagene autoleucel) drug product for treatment of r/r ALL is a patient-specific suspension of autologous CAR-positive T cells at a dose of 1 x 10^6 cells/kg in approximately 68 mL. The formulation contains 5% dimethylsulfoxide (DMSO) and (b) (4) of human albumin. DMSO and human albumin are immunogenic. The risk of hypersensitive reactions to these components warrants assessment in the safety review.

All KTE-X19 products used in ZUMA-3 were produced employing a single major manufacturing process (X19), so data from all subjects in the trial are relevant to the review. A small number of subjects from the Phase 1 portion of the study had product formulated in 40 mL rather than 68 mL. The impact of formulation volume on efficacy and safety is discussed in Sections 8.1 and 8.2, respectively.

The CMC review team concluded that the stability data submitted in this sBLA support the approved long-term and in-use storage shelf life for KTE-X19. The release acceptance criteria are uniform across indications except for the dose, which is higher for the MCL indication. CMC stated that the Applicant has the capability for the expected increase in manufacturing capacity

and that they also have the appropriate chain of Identity/Chain of Custody (COI/COC) system to ensure that indication-specific dose is formulated. Therefore, the CMC review team concluded that this BLA efficacy supplement provides adequate manufacturing data and information to support marketing of KTE-X19 for adults with r/r pre-B ALL and recommends approving the supplement.

4.3. Devices and Companion Diagnostic Issues

The FDA's Assessment:

The Applicant is seeking to include in labeling a description of the minimal residual disease (MRD) testing results for the pivotal cohort in ZUMA-3. In this study, MRD was measured by (b) (4) The CDRH Reviewer noted that the submission did not include sufficient data to establish the analytical validity of the assay for the level of MRD needed to support the proposed labeling.[6]

5 Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's Position:
Reference is made to the original KTE-X19 BLA 125703 approved on 24 July 2020. The primary nonclinical data supporting the development of KTE-X19 leveraged data generated in support of axicabtagene ciloleucel, Kite's first anti-CD19 CAR T-cell product. KTE-X19 uses the same replication-incompetent murine γ-retroviral vector, anti-CD19 CAR transgene, and producer clone as is used in the manufacture of axicabtagene ciloleucel. The initial in vitro characterization studies and nonclinical proof-of-concept studies were conducted by investigators at the (b) (4) ; Investigational New Drug (b) (4) and subsequent characterization studies were conducted collaboratively by Kite and the (b) (4) or independently by Kite. Additional nonclinical toxicology data (including vector integration site [VIS] data) have been provided with this sBLA. Overall, the nonclinical pharmacology/toxicology profile for KTE-X19 has not changed, and results support the treatment of patients with r/r B-ALL.

Genetic toxicology - Clinical studies employing human T cells transduced with a γ-retroviral vector have not revealed any cases of human genotoxicity leading to malignancy to date. The literature supporting this finding is further described in m4.2.3.3.2 Genotoxicity In Vivo Report, Section 2.3.

[6] BLA 125703/91 Consult Review by Matthew J. Butcher, PhD, dated July 29, 2021.

Although the γ-retroviral vector cannot replicate, VIS data were assessed in CAR T-cell products manufactured from healthy donors' T cells. These T-cell products were manufactured with the same retroviral vector used in the manufacture of KTE-X19. Results showed that VIS were found preferentially near transcriptional start sites of T-cell-related genes that were transcriptionally active. These results indicate that T-cell transformation due to vector-mediated insertional mutagenesis would be an extremely rare event that likely requires multiple additional contributing factors beyond the integration site of the viral vector.

No carcinogenicity or reproductive and developmental toxicology studies were included in the original submission and no new information is provided in the current submission.

The FDA's Assessment:
FDA agrees with the Applicant's position. No new nonclinical data were submitted or are in need of review in the current submission.

6 Clinical Pharmacology

6.1. Pharmacology and Clinical Pharmacokinetics

Data:

Clinical pharmacology data are provided in m5.3.4.2 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report and in m272 Summary of Clinical Pharmacology.

Pharmacokinetics in Patients With r/r B-ALL

The median time to peak of anti-CD19 CAR T cell levels in blood was 15 days after the KTE-X19 infusion. By Month 6, median anti-CD19 CAR T-cell levels in blood declined to undetectable levels in 22 of 28 subjects (79%) with evaluable samples; by Month 12, levels declined to undetectable levels in 18 of 20 subjects (90%) with evaluable samples.

Anti-CD19 CAR T-cell levels in blood (median peak and area-under-the-curve from Day 0 to Day 28 [AUC_{0-28}]) were numerically lower in subjects < 65 years of age compared with subjects ≥ 65 years of age; due to the small number of subjects who were ≥ 65 years of age in Phase 2, results should be interpreted with caution. Anti-CD19 CAR T-cell levels were numerically lower in females than in males (m5.3.4.2, Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.2.1; ADCART, ADSL).

Pharmacodynamics

Serum Biomarkers: A panel of 18 analytes (representing homeostatic, inflammatory, and immune-modulating cytokines, chemokines, and immune-effector molecules) were preselected from a larger analyte panel (N=40) for examination based on their known involvement in mediating the antitumor activity of CAR T cells and treatment-related toxicity {Brudno 2018, Kochenderfer 2013, Kochenderfer 2017, Neelapu 2017}. Most analytes were elevated by ≥ 2-fold on Day 3 or Day 7 relative to baseline. In general, serum analytes peaked between 7 and 8 days after KTE-X19 infusion, and decreased to baseline levels by Week 4 in most subjects (m5.3.4.2, Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.2.2; ADCYTO, ADSL).

Peripheral B cells: B-cell aplasia is an on-target/off-tumor pharmacodynamic effect of KTE-X19; thus, B-cell proportions in peripheral blood mononuclear cells (PBMCs), as a percentage of viable leukocytes, were monitored over time. B cells were detectable in 47 of 49 tested subjects (95.9%) at baseline (median B-cell percentage was 22.7%), in 9 of the 36 tested subjects (25.0%) at Day 28 (median B-cell percentage was 0.05%), and in all 22 tested subjects (100.0%) at Month 12 (median B-cell percentage was 20.1%) (m5.3.4.2, Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.2.3; ADSL, ADLB).

The pharmacologic profile of KTE-X19 in subjects with r/r B-ALL is consistent with the known mechanism of action of T-cell mediated killing of CD19+ target cells and with the previous findings in adult patients with r/r MCL that were submitted in the original BLA 125703.

Pharmacokinetics and Associations

In Phase 2, the median peak anti-CD19 CAR T cell levels and AUC_{0-28} were the highest in subjects who achieved a CR by central assessment, followed by subjects who achieved a CRi, subjects who had blast-free hypoplastic or aplastic bone marrow, and subjects who had no response (m5.3.4.2, ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.3.1.1.1 Table 18; ADCART, ADEFF, ADSL).

Associations between anti-CD19 CAR T-cell levels in blood (median peak and AUC_{0-28}) with ongoing response to treatment are described in Section Dose/Dose Response.

No association was observed between anti-CD19 CAR T-cell levels in blood (median peak and AUC_{0-28}) with frequency of worst Grade 3 or higher relative to worst Grade 2 or lower CRS (m5.3.4.2, Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.3.1.3.1.1, Figure 7, Figure 8; ADAE, ADCART, ADSL). A potential association was observed between anti-CD19 CAR T-cell levels (median peak and AUC_{0-28}) with frequency of worst Grade 3 or higher relative to worst Grade 2 or lower neurologic AEs (m5.3.4.2,

Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.3.1.3.2.1, Figure 9, Figure 10; ADAE, ADCART, ADSL).

Among subjects who experienced worst Grade 3 or higher CRS compared with subjects who experienced worst Grade 2 or lower CRS, median peak serum levels were numerically higher for ferritin, granzyme B, IFN-γ, IL-2Rα, IL-6, IL-8, IL-10, IL-15, TNF-α, and GM-CSF. Among subjects who experienced worst Grade 3 or higher neurologic AEs compared with subjects who experienced worst Grade 2 or lower neurologic AEs, median peak serum levels were numerically higher for IL-1RA and IL-6 (m5.3.4.2, Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.3.3.1, Table 26, Table 27; ADAE, ADCYTO, ADSL).

Anti-CD19 CAR T-cell expansion was not impaired by the use of tocilizumab and/or corticosteroids for toxicity management, however, ZUMA-3 study was not designed to test the impact of tocilizumab and/or corticosteroids on the expansion kinetics of KTE-X19 (m5.3.4.2, Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.2.1.3.4, Table 10; ADCM, ADCART, ADSL).

6.2. General Dosing

The Applicant's Position:
The proposed lymphodepleting chemotherapy regimen and KTE-X19 dose for adult patients is based on the positive benefit-risk profile observed in subjects with r/r B-ALL (current sBLA). The recommended treatment regimen for patients with B-ALL is a lymphodepleting chemotherapy regimen of fludarabine 25 mg/m^2/day administered intravenously (IV) on Day −4, Day −3, and Day −2 and cyclophosphamide 900 mg/m^2/day administered IV on Day −2 prior to the infusion of KTE-X19 on Day 0. The dose of 1 x 10^6 anti-CD19 CAR T cells/kg was selected as the recommended dose for KTE-X19 based on ZUMA-3 Phase 1 results where the dose demonstrated the highest efficacy, a manageable safety profile, and the most favorable benefit-risk profile across the doses evaluated. For subjects weighing > 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR T cells was administered. No alternative dosing regimens are proposed.

6.3. Summary

The Applicant's Position:
KTE-X19 has demonstrated efficacy in treating r/r MCL, as described in the original BLA, and the mechanism of action of KTE-X19 is well described {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017, Neelapu 2017}. The pharmacokinetic and pharmacodynamic profiles of KTE-X19 in subjects with B-ALL are generally consistent with the known mechanism of action of anti-CD19 CAR T cells and with prior published reports of CD19-directed CD28/CD3 ζ CAR T cells {Kochenderfer 2017, Neelapu 2017, Wang 2020}.

The FDA's Assessment:

Below is a summary of KTE-X19 Pharmacokinetics/Pharmacodynamics (PK/PD) data per the Clinical Pharmacology Reviewer:

Pharmacokinetics

The following dose levels of KTE-X19 were evaluated in the Phase 1 of Study ZUMA-3: 0.5 x 10^6 anti-CD19 CAR T cells/kg (68 mL), 0.5 x 10^6 anti-CD19 CAR T cells/kg (40 mL), 1 x 10^6 anti-CD19 CAR T cells/kg, 1 x 10^6 anti-CD19 CAR T cells/kg (with modified toxicity management), and 2 x 10^6 anti-CD19 CAR T cells/kg.

After the initial single dose infusion of KTE-X19, KTE-X19 cells exhibited an initial rapid expansion phase followed by bi-phasic decline. KTE-X19 achieved peak levels in blood between 8 to 15 days post-infusion in subjects with B-ALL. Across dose levels evaluated, there's no clear dose-response for KTE-X19 exposure (Cmax and AUC0-28d). Median peak anti-CD19 CAR T-cell levels were highest in subjects treated at the 1.0 x 10^6 dose level with modified toxicity management (37.7 cells/µL), followed by subjects treated at the following dose levels (from the highest to the lowest): 1.0 x 10^6 cells/kg with original toxicity management (26.5 cells/µL); 0.5 x 10^6 cells/kg (68 mL; 23.1 cells/µL); 2.0 x 10^6 cells/kg (8.6 cells/µL); and 0.5 x 10^6 cells/kg (40 mL; 4.7 cells/µL). A similar pattern was observed for the median AUC0-28d.

All subjects in Phase 2 were treated at 1 x 10^6 anti-CD19 CAR T cells/kg dose according to the modified toxicity management guidance. The PK profiles of KTE-X19 in Phase 2 were similar to Phase 1 1e6 dose cohorts. Median peak anti-CD19 CAR T-cell levels and AUC0-28d for subjects in Phase 2 were 20.6 cells/µL and 220.60 cells/µL*days, respectively. Median Tmax was 15 days post-dose. IFN-γ levels in co-culture showed a potential positive association with post-infusion peak level of anti-CD19 CAR T cells. At the dose level of 1.0 x 10^6 cells/kg (n=78), levels of percentage of blast at screening were negatively associated with KTE-X19 expansion.

Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with KTE-X19. Subjects who received both tocilizumab and corticosteroids had higher KTE-X19 exposure than subjects who received either medication alone or neither medication. These observations are confounded by the fact that the need for tocilizumab and/or corticosteroids was triggered by toxicity, which was associated with higher KTE-X19 exposures.

After KTE-X19 infusion, substantially higher expansion (median values of Cmax and $AUC_{0\text{-}28d}$) were observed in responders (CR+CRi) compared to nonresponders. Among subjects in efficacy

analysis set (ZUMA-3 Phase 2, N=54), median peak anti-CD19 CAR T-cell levels over time by best overall response per independent review was 38.35 cells/µL (range: 1.31 to 1,533.40 cells/µL; n = 32) in subjects who had OCR, and 0.49 cells/µL (range: 0.00 to 183.50 cells/µL, n = 17) in subjects who had non-complete remission. The median AUC_{0-28} in subjects who had OCR was 424.03 cells/µL*days (range: 14.12 to 19,390.42 cells/µL*days; n = 32) vs 7.9 cells/µL*days in subjects who had non-complete remission (range: 0.00 to 889.0 cells/µL*days; n=17).

Higher KTE-X19 exposure (Cmax and AUC0-28d) was associated with higher incidence of grade 2 and above CRS and NT.

At the dose level of 1.0 x 10^6 cells/kg (n=78), the median Cmax and AUC0-28d of KTE-X19 in subjects with Grade 2 or higher CRS were 6.9-fold and 5.3-fold comparing to that in subjects with Grade 1 or no CRS. The median Cmax and AUC0-28d of KTE-X19 in subjects with Grade 2 or higher NT were 2.5-fold and 2.6-fold comparing to that in subjects with Grade 1 or no NT.

Pharmacodynamics
After KTE-X19 infusion, majority of subjects had B-cell aplasia. B-cell recovery was observed at Month 3. At Month 12, B-cell recovery was observed in all evaluable subjects.

Serum analytes (cytokines, chemokines, and other molecules) generally peaked between 7-8 days after KTE-X19 infusion and decreased to near-baseline levels by week 4. Following associations were observed between serum analytes levels and severe adverse events (CRS and neurological events):

- After KTE-X19 infusion, substantial elevation in serum levels were observed in subjects with Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following biomarkers: ferritin, granzyme B, INF-γ, IL-2Rα, IL-6, IL-8, IL-10, IL-15, TNF-α, and GM-CSF.
- After KTE-X19 infusion, substantial elevation in serum levels were observed in subjects with Grade 3 or higher neurologic event compared to subjects with Grade 2, Grade 1 or no neurologic event for following biomarkers: IL-1RA and IL-6.

Reviewer Comment: *The analyses performed by the Clinical Pharmacology Reviewer demonstrate that across all dose levels evaluated in the Phase 1 and Phase 2, the KTE-X19 exposure was not dose-related. In addition, the analyses of CRS and NT effects and tocilizumab and corticosteroids use on KTE-X19 exposure only show an association and not a causal relationship. Thus, it is unclear whether the subjects who received tocilizumab and corticosteroids have a higher exposure because of the medications or if subjects with higher exposure have worse CRS and NT that required the use of tocilizumab and corticosteroids.*

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:
Studies included in this sBLA are summarized in Table 5.

Table 5 Kite - Listing of Clinical Trials Relevant to This sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Primary Study to Support Efficacy and Safety								
KTE-C19-103 (ZUMA-3)	NCT 02614066	Phase 1/2 multicenter, open-label safety and efficacy	Lymphodepleting chemotherapy: fludarabine 25 mg/m^2/day for 3 days plus cyclophosphamide 900 mg/m^2/day on Day −2 prior to KTE-X19 infusion on Day 0. KTE-X19: Phase 2; 1 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing more than 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR T cells may be administered.	Primary: OCR (CR+CRi) rate Secondary: MRD− rate, DOR, OCR rate (IA), allo-SCT rate, OS, RFS rate, incidence of AEs, incidence of CTCAE grade changes in laboratory values, changes over time in EQ-5D and VAS scores, incidence of antibodies to anti-CD19 CAR	KTE-X19 is administered as a single infusion. Subjects will be followed for survival for up to approximately 15 years after the last subject receives their KTE-X19 infusion.	Phase 1 54 leukapheresed; 45 treated Phase 2 71 leukapheresed; 55 treated	Adult subjects with r/r B-ALL, with morphological disease in the bone marrow (> 5% blasts)	29 Centers[a] 5 Countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
KTE-C19-102 (ZUMA-2)[b]	NCT 02601313	Phase 2 multicenter, open-label safety and efficacy	Lymphodepleting chemotherapy: fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day for 3 days prior to KTE-X19 infusion on Day 0. KTE-X19: Cohort 1; 2 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing more than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells may be administered.	Primary: ORR (Cohort 1) Secondary: Best objective response, ORR and best objective response (IA), DOR, PFS, OS, incidence of AEs, incidence of CTCAE grade changes in laboratory values, changes over time in EQ-5D and VAS scores, incidence of antibodies to anti-CD19 CAR	KTE-X19 is administered as a single infusion. Subjects will be followed for survival for up to approximately 15 years after the last subject receives their KTE-X19 infusion.	91 leukapheresed; 82 treated	Adult subjects with r/r MCL, with no evidence of central nervous system lymphoma	26 Centers[a] 4 Countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
KTE-C19-104 (ZUMA-4)[c]	NCT 02625480	Phase 1/2 multicenter, open-label safety and efficacy	Lymphodepleting chemotherapy: fludarabine 25 mg/m^2/day for 3 days plus cyclophosphamide 900 mg/m^2/day on Day −2 prior to KTE-X19 infusion on Day 0. KTE-X19: 1 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing more than 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR T cells may be administered.	Primary ALL cohort: OCR (CR+CRi) rate Primary NHL cohort: ORR (CR+PR) rate Secondary ALL cohort: MRD− rate, DOR, OCR rate (IA), allo-SCT rate, OS, RFS rate, incidence of AEs, incidence of CTCAE grade changes in laboratory values, changes over time in PRO scores, incidence of antibodies to anti-CD19 CAR Secondary NHL cohort: DOR, OS, PFS, incidence of AEs, incidence of CTCAE grade changes in laboratory values, changes over time in PRO scores (Phase 2 only), incidence of antibodies to anti-CD19 CAR	KTE-X19 is administered as a single infusion. Subjects will be followed for survival for up to approximately 15 years after receiving their KTE-X19 infusion.	48 leukapheresed; 36 treated	Pediatric and adolescent subjects with r/r B-ALL or NHL	17 Centers[a] 3 Countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
KTE-C19-108 (ZUMA-8)[d]	NCT 03624036	Phase 1 multicenter, open-label safety and tolerability	Lymphodepleting chemotherapy: fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day for 3 days prior to KTE-X19 infusion on Day 0. KTE-X19: Cohorts 1, 3, 4a; 1 x 10^6 anti-CD19 CAR T cells/kg, Cohort 2; 2 x 10^6 anti-CD19 CAR T cells/kg	Primary: incidence of DLTs Secondary: ORR (CR/CRi/PR) per IA as defined by IWCLL 2018 criteria for selected safety dose cohort, incidence of AEs, levels of antibodies to anti-CD19 CAR	KTE-X19 is administered as a single infusion. Enrolled subjects will be followed in the long-term follow-up period for safety, survival and disease status, if applicable, for up to 15 years.	10 leukapheresed; 9 treated	Adult subjects with r/r CLL and SLL previously treated with 2 lines of therapy	10 Centers[a] 2 Countries
KT-US-472-0118 (ZUMA-18)[e]	NCT 04162756	Expanded access study, multicenter, open-label safety and efficacy	Lymphodepleting chemotherapy: fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day for 3 days prior to KTE-X19 infusion on Day 0. KTE-X19: Cohort 1; 2 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing more than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells may be administered.	Endpoints cohort 1 and 2: incidence of AEs and changes in laboratory values by toxicity grade, ORR (CR+PR) per standard of care, OS Additional endpoints cohort 2 only: levels of antibodies to anti-CD19 CAR, levels of cytokines	KTE-X19 is administered as a single infusion. Subjects will be followed for survival for up to approximately 15 years after the last subject receives their KTE-X19 infusion.	25 leukapheresed; 21 treated	Adult subjects with r/r MCL who have received at least 1 prior therapy	8 Centers[a] 1 Country

Data cutoff date = 09Sep2020

Abbreviations: AE, adverse event; B-ALL, B-cell precursor acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of remission; IA, investigator assessment; MCL, mantle cell lymphoma; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; OCR, overall complete remission; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; r/r, relapsed/refractory; RFS, remission-free survival; SCT, stem cell transplant; SLL, small lymphocytic leukemia; US, United States

a Only centers that enrolled subjects are included.
b Ten subjects enrolled in ZUMA-2 and treated with axicabtagene ciloleucel were not included in KTE-X19 safety analyses.
c One subject with NHL enrolled in ZUMA-4 and treated with KTE-X19 at a target dose of 1×10^6 cells/kg was not included in KTE-X19 safety analyses.
d No subjects with r/r SLL in ZUMA-8 were treated with KTE-X19 by the data cutoff date.
e Only subjects in ZUMA-18 Cohort 1 were included in the safety analyses.

The FDA's Assessment:
FDA agrees with the Applicant's listing of clinical trials relevant to this submission.

7.2. Review Strategy

The FDA's Assessment:
The ZUMA-3 study served as the primary basis for the clinical review. The Applicant submitted supportive data from four additional studies as listed above. The key material used in the review of the efficacy and safety includes:

- sBLA 125703/91 submission
- Prior regulatory history
- Applicant's response to the review team's several information requests (IR)
- Proposed labeling
- Relevant published literature

Safety and efficacy analyses were performed using JMP 15 (SAS Institute, Inc.), MedDRA Adverse Events Diagnostic (MAED) v3.0 (FDA, Silver Spring, MD), and Empirica Signal 8.0.1.0.316 (Oracle, Redwood Shores, CA). Data cutoff date was 09 September 2020.

Efficacy:
The determination of efficacy was based primarily on the analysis of data submitted for the 54 subjects who were enrolled and treated in ZUMA-3 Phase 2 study and who had documented disease at baseline post-bridging therapy. FDA efficacy evaluable population excluded one subject (Subject ID (b) (6)) from that of the Applicant's (N=55) because the subject lacked presence of BM blasts at baseline disease assessment post-bridging chemotherapy. Data from the remainder of the subjects treated on ZUMA-3 are supporting.

Safety:
The main safety analysis set included all subjects who received KTE-X19 at a target dose of 1 x 10^6 anti-CD19 CAR T cells/kg, which is the proposed dose. The main safety analysis set consisted of 78 subjects (23 subjects from the Phase 1 portion of the study and 55 subjects from the Phase 2). Data from the remainder of the subjects in the ISS are supporting. Details of the approach to the review of safety are described in Section 8.2.1.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

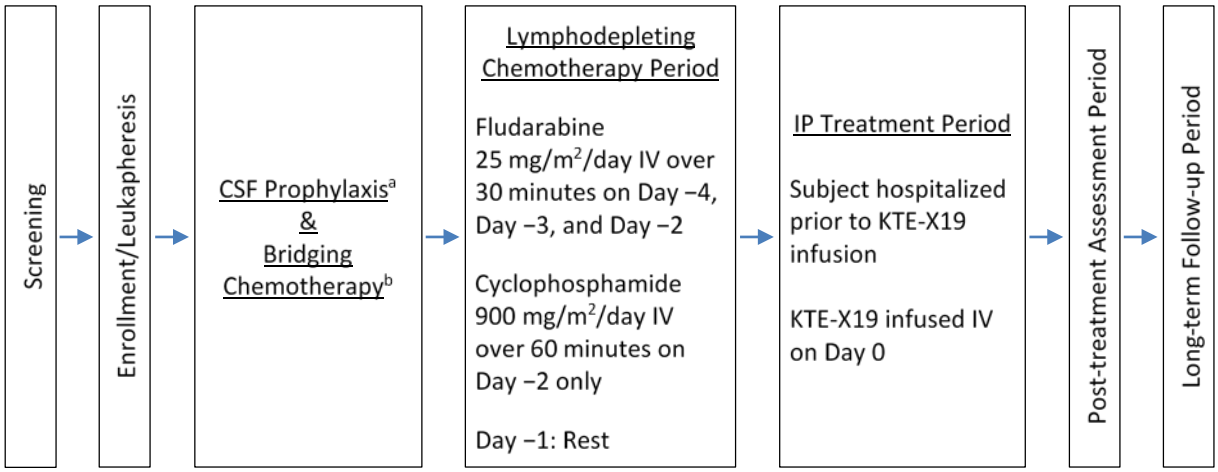
8.1.1. ZUMA-3

Trial Design

The Applicant's Description:

The study design of ZUMA-3 is summarized above in Table 5. The study schema is provided in Figure 1.

Figure 1 Kite - ZUMA-3 Study Schema



Abbreviations: CSF, cerebrospinal fluid; IP, investigational product; IV, intravenous
Note: The terms "conditioning chemotherapy" and "lymphodepleting chemotherapy" are considered interchangeable.
a CSF prophylaxis (administered any time during screening through 7 days prior to KTE X19 infusion): All subjects were to receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines. CSF prophylaxis could be administered with the screening lumbar puncture.
b Bridging chemotherapy (administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever was shorter, prior to initiating lymphodepleting chemotherapy): Bridging chemotherapy was recommended for all subjects, particularly those subjects with high disease burden at screening (M3 marrow [> 25% leukemic blasts] or ≥ 1,000 blasts/mm^3 in the peripheral circulation).
Source: m5.3.5.2, ZUMA-3 Primary Analysis Clinical Study Report (CSR), Figure 3B.

The FDA's Assessment:

ZUMA-3 study is a Phase 1/2 multi-center study evaluating the safety and efficacy of KTE-X19 in adult Subjects with r/r ALL.

Eligibility: Eligible subjects were 18 years of age or older with r/r B-ALL, defined as one of the following: primary refractory disease, first relapse if first remission was ≤ 12 months, r/r disease after 2 or more lines of systemic therapy, or r/r disease after allogeneic stem cell transplant (allo SCT) provided the subject was at least 100 days from transplant at the time of enrollment and off of immunosuppressive medications for at least 4 weeks prior to enrollment. Subjects were required to have morphological disease in the bone marrow (> 5% blasts) at the time of enrollment.

Subjects with Philadelphia chromosome (Ph)+ disease were eligible if they were intolerant to tyrosine kinase inhibitor (TKI) therapy or if they had r/r disease despite treatment with at least 2 different TKIs. In subjects previously treated with blinatumomab, CD19 tumor expression on blasts obtained from bone marrow or peripheral blood must have been documented after completion of the most recent prior line of therapy. If CD19 expression was quantified, then blasts must have been ≥ 90% CD19+. Subjects with central nervous system (CNS)-1 disease (no detectable leukemia in the CSF) and those with CNS-2 disease (defined as detectable cerebrospinal blast cells in a sample of CSF with < 5 white blood cells (WBCs) per mm3) without clinically evident neurological changes were eligible to participate in the study. Subjects with CNS-2 disease with neurological changes and subjects with CNS-3 disease (defined as detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 WBC per mm3) with or without neurological changes were excluded from the study.

Treatment: FDA agrees with the Applicant's description of treatment in the Figure above. Subjects were enrolled in the study when they underwent leukapheresis. Subjects received a single infusion of KTE-X19, and the main analyses of efficacy and safety are based on outcomes following this infusion. In instances where subjects initially achieved remission and subsequently progressed, subjects were eligible for a second course of lymphodepleting chemotherapy and KTE-X19. Outcomes following retreatment were analyzed separately.

Monitoring: For efficacy, subjects were to be evaluated for disease response by the site investigator at the times indicated in the schedule of assessments (see Table 49). Disease response was evaluated by the investigator using the overall disease response classification as shown in Table 51 and Table 52 and included bone marrow evaluations, as well as imaging for subjects with known non-CNS extramedullary disease at baseline. All subjects in Phase 2 were also to be evaluated for disease response by an independent review committee (central assessment). The central assessment of disease response used the same overall disease response classification shown in Table 51 and Table 52, with the exception that an overall disease response of CR, CRi, or CRh was to

be adjusted for a more conservative assessment if platelet transfusions or G-CSF had been administered within 7 days before the disease assessment.

Subjects were to be hospitalized for treatment with KTE-X19 and remain in the hospital for a minimum of seven days after treatment. Subjects were to remain hospitalized until all KTE-X19-related nonhematological toxicities had returned to Grade 1 or lower or baseline. Subjects were also to remain hospitalized for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing central neurologic toxicity if the event severity was higher than Grade 1 or if deemed necessary by the treating investigator.

Subjects were to undergo safety assessments throughout the conduct of the study, as summarized in the schedule of assessments (Appendix Table 49). Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, neurological assessments, electrocardiogram, echocardiogram, physical examinations, and testing for RCR and antibodies to the anti-CD19 CAR. Details on long-term follow-up assessments are in Appendix Table 50.

Study Endpoints

The Applicant's Description:

Primary endpoint: The primary efficacy endpoint was the OCR rate, defined as the combined rate of CR + CRi in adult subjects with r/r B-ALL per central assessment in the modified intent-to-treat (mITT) analysis set in Phase 2. The primary analysis was planned to occur when the overall study enrollment was complete and the last treated subject in the mITT analysis set had had the opportunity to complete the Month 6 disease assessment. At the time of the data cutoff date for the primary analysis, all subjects in the mITT analysis set had had the opportunity to be followed for at least 10 months after the KTE X19 infusion.

Secondary endpoints: Secondary endpoints included MRD status, OCR rate by investigator assessment, allo-SCT rate, DOR, RFS rate, OS, incidence of AEs and clinically significant changes in laboratory values, changes over time in European Quality of Life-5 Dimensions (EQ-5D) and visual analogue scale (VAS) scores, and incidence of antibodies to the anti-CD19 CAR.

Exploratory endpoints: Select exploratory endpoints included levels of anti-CD19 CAR T cells in blood and levels of cytokines in serum.

The FDA's Assessment:
For the purposes of regulatory decision-making, FDA has accepted CR within 3 months

from infusion and durability as a measure of clinical benefit. The endpoint was not prespecified in the protocol. See Section 8.1.3 for further discussion.

Statistical Analysis Plan and Amendments

The Applicant's Description:
ZUMA-3 used a single-arm design to test for an improvement in OCR rate. A sample size of 50 subjects treated with KTE-X19 in Phase 2 provided approximately 93% power to distinguish between an active therapy with a 65% true OCR rate from a therapy with a OCR rate of 40% or less, with the one-sided alpha level of 0.025. A step-down test of the secondary endpoint MRD− rate was performed against a control MRD− rate of 30% if the testing of the OCR rate was significant. An exact binomial test was used to test the statistical hypotheses. The primary analysis was conducted when 55 subjects treated at the 1.0×10^6 anti-CD19 CAR T cells/kg dose level in Phase 2 mITT analysis set had had the opportunity to be followed for at least 10 months after KTE X19 infusion.
The rationale for a prespecified 40% OCR historical control rate was informed by rates observed in published studies of second-line or later chemotherapy and SCT regimens and in pivotal studies of blinatumomab. The blinatumomab studies, which included patient populations similar to those enrolled in ZUMA-3, resulted in CR/complete remission with partial hematologic recovery (CRh) rates of approximately 42%; the CR rates were 32.4% in the Phase 2 study and 33.6% in the Phase 3 TOWER study.
By comparison, standard-of-care chemotherapy for subjects in the TOWER study yielded a CR rate of 15.7% and a CR/CRh rate of 20.1% {BLINCYTO 2019, Kantarjian 2017}.

To provide a contemporary assessment of outcomes in r/r ALL, a meta-analysis of OCR and CR rate was conducted based on a systematic review of studies published as of November 2020 that described outcomes for adult subjects with r/r ALL treated with currently approved, standard-of-care treatments, namely blinatumomab, inotuzumab, tyrosine kinase inhibitors (TKIs), and chemotherapy regimens. Although the definitions used for CR across studies were generally comparable and consistent with ZUMA-3, the reviewed studies varied widely in their definitions of CRi and, consequently, their definitions of OCR. Thus, the OCR analysis included only studies that employed the same CRi definition as that used in ZUMA-3.

Overall, 2 treatment arms from 1 study (TOWER) were included in the meta-analysis of OCR, with a pooled estimate of OCR rate of 32%. Since the CRi definitions in the trials were too heterogenous to allow a pooled estimate, a subsequent analysis was conducted on the more consistent CR endpoint using 15 treatment arms across 12 studies. The resulting pooled CR rate estimate was 30% based on the random-effects

model. Based on 13 treatment arms across 10 studies with available OS data, the estimated median OS was 6.9 months for the random-effects model.

Additional details regarding the statistical analysis plan are provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 7.7.

The FDA's Assessment:
Per protocol, the primary analysis was planned to occur when the overall study enrollment was complete and the last treated subject in the mITT analysis set had had the opportunity to complete the Month 6 disease assessment. At the time of the data cutoff date for the primary analysis, all subjects in the Applicant's mITT analysis set had the opportunity to be followed for at least 10 months after the KTE-X19 infusion.

The Applicant's prespecified boundaries for the study success were found to be reasonable and FDA agrees with the Applicant description of the statistical analysis methods for the efficacy endpoints. The Applicant provided a copy of the final SAP version 2.0 dated 06 July 2020 in Appendix 16.1.9.

Reviewer comment: *The reviewer found discrepancy in the definition of DOR and censoring assessments among the clinical protocol, SAP and CSR. The Applicant clarified in response to IR that the DOR definition in the SAP is the accurate definition which is: "For primary analysis of DOR, the derivation will be from the first CR/CRi, per independent review, to relapse or death from any cause in the absence of relapse. Should the subject not relapse or die, the DOR will be censored at the last disease assessment prior to the data cutoff date, or new anti-cancer therapy (excluding TKI as in the primary analysis of DOR, TKI is not considered as the new anti-cancer therapy), or allogeneic SCT.*

Protocol Amendments

The Applicant's Description:
The original protocol, dated 07 May 2015, was amended 6 times during the study. The original protocol, Amendment 6, and summary of changes documents for Amendments 1 through 6 are provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 16.1.1.1. A summary of changes for each amendment is provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 7.8.1.1. Overall, the changes made to the protocol did not impact the integrity of the study.

The FDA's Assessment:
Key changes from the original protocol included addition of different KTE-X19 dose

cohorts and modification to the toxicity management guidance (e.g., administration of corticosteroids for lower grades of CRS and neurologic AEs).

Specifically, based on the safety and efficacy observations from the first several subjects treated in ZUMA-3 Phase 1, the ZUMA-3 safety review team (SRT) recommended the exploration of the safety profile of the 1 x 10^6 anti-CD19 CAR T cells/kg dose level with the implementation of modified toxicity management recommendations (administration of corticosteroids for lower grades of CRS and neurologic AEs), and additional subjects were enrolled at this dose level (starting from 12 June 2017 onwards). The safety profile observed in subjects who received the 1 x 10^6 anti-CD19 CAR T cells/kg dose and earlier intervention with corticosteroids was considered by the SRT to be favorable, without a significant decrease in efficacy. Therefore, the dose of 1 x 10^6 anti-CD19 CAR T cells/kg was considered the recommended Phase 2 dose, and all subjects in Phase 2 were treated according to the modified toxicity management guidance.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:
The Kite Quality Assurance group conducted 3 compliance audits of sites during the course of the study. Site audit certificates are provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 16.1.8.

The Applicant's Position:
All studies conducted in the KTE-X19 development program met International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. For studies conducted under a US investigational new drug application, investigators were required to ensure adherence to the basic principles of GCP as outlined in US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), as well as other local legislation (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 5.2).

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

Certificates of audit for three investigative sites (Site 031 "University of Chicago; Principal Investigator (PI): Michael Bishop", Site 002 "Moffitt Cancer Center; PI: Bijal Shah", and Site 051 "Swedish Cancer Institute; PI: John Pagel) that underwent

compliance audits by the Applicant for this study were included in the Applicant's sBLA submission and were provided in Appendix 16.1.8 of the CSR.

The Applicant collected a Form 1572 from investigators at each foreign clinical site. For the sites in Germany with three investigators who were unable to sign Form 1572 due to local regulatory requirements, FDA issued a Waiver Granted letter dated 04 December 2019 (under IND 16675) and requested collection of unsigned Forms 1572 for the investigators. Unsigned Forms 1572 were collected and submitted to the IND accordingly.

After consideration of factors including subject enrollment and outcomes, protocol deviations, financial disclosures, geographic location, and inspection history, three clinical sites (covering approximately 30% of the subjects enrolled in ZUMA 3 Study) were selected for inspection and verification of submitted data by FDA's Bioresearch Monitoring (BIMO) team:

- Site 002: Moffitt Cancer Center; PI: Bijal Shah
- Site 029: Emory University Hospital; PI: Martha Arellano
- Site 031: University of Chicago; PI: Michael Bishop

Overall, the inspections verified the data reported in the sBLA, including but not limited to subject eligibility, protocol deviations, study drug administration, primary efficacy endpoint, and adverse events for all subjects enrolled at the inspected clinical sites. No Form FDA 483 was issued for three sites.

Per the BIMO Reviewer for Site 031: the FDA investigator discovered several discrepancies between the source data and the data listings submitted to the FDA during their review. The data in the electronic data capture (EDC) system matched the data listings and it appeared that these discrepancies were due to data entry errors by the staff when the source data was manually entered in the EDC. No inspectional observations were noted during the inspection and no Form FDA 483s were issued to the clinical investigator. The inspection was classified as No Action Indicated (NAI).

Reviewer comment: *The discrepancies and data errors were considered minor and included for example, missed documentation of one medication for CSF prophylaxis, wrong dose and wrong date of bridging chemotherapy, missed documentation of red blood cell transfusions. These data errors were considered not clinically significant and did not impact either the results of the Reviewer's analyses or conclusions.*

Data Quality and Integrity

The Applicant's Position:
All data were collected via an electronic case report form (CRF) system, and source document verification of CRF data was performed at regular intervals during the study. Protocol adherence, accuracy, and consistency of study conduct and data collection with respect to local regulations was confirmed. Investigators assured cooperation and compliance with the monitoring visits. Site audits were to include an inspection of the facility(ies); review of subject and study-related records; and compliance with protocol requirements, ICH/GCP, and applicable regulatory policies. Additional information is provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 7.6.

The FDA's Assessment:
After FDA's adjudication of efficacy data, FDA requested that the Applicant submits new datasets that reflect FDA's adjudication. The Applicant submitted the updated datasets (ADSLFDA, ADBASEFDA, ADEFFFDA and ADTTEFDA, on 30 July 2021 under SN 0123. Based on further review of Subject (b) (6), the Applicant submitted updated ADTTEFDA file on 11 August 2021 under SN 0128 to reflect FDA's adjudication. In the ADTTEFDA, the variables FDAADJRS, FDAADJR1 and FDAADJR2 were added for the FDA adjudication comments. The FDA-adjudicated responses were used for FDA's analyses of efficacy.

Financial Disclosure

Data:
Kite Pharma has adequately disclosed financial interests/arrangements with clinical investigators in accordance with the guidance for industry. Financial disclosure information was submitted in m1.3.4, Financial Certification and Disclosure for investigators involved in ZUMA-3. Additional details are provided in the Appendix Section 16.2.

The FDA's Assessment:
See Section 16.2 for details.

Patient Disposition

Data:
In ZUMA-3 Phase 2, a total of 71 subjects were enrolled (ie, underwent leukapheresis); of these, 57 subjects received lymphodepleting chemotherapy, and 55 subjects received KTE-X19 (these 55 subjects constituted the mITT and safety analysis sets). Two subjects

were not treated with KTE-X19 after receiving lymphodepleting chemotherapy.
For subjects treated in Phase 2, the median actual follow-up time from the KTE-X19 infusion was 12.4 months (range: 0.3 to 22.1 months), and the median potential follow-up time was 16.4 months (range: 10.3 to 22.1 months); all subjects had > 9 months of potential follow-up, and 93% had ≥ 12 months of potential follow-up (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Table 9; ADSL, ADEX).

The Applicant's Position:
The number of subjects enrolled and treated with KTE-X19 is sufficient to evaluate the efficacy and safety of this treatment in subjects with r/r B-ALL.

The FDA's Assessment:
The study was conducted at a total of 32 study centers in the US, Canada, France, Germany, and the Netherlands. First subject was enrolled on 07 March 2016 and the last observation for the primary analysis was 09 September 2020.
A summary of the analysis population sets is presented in Table 6 below.

Table 6 FDA - ZUMA-3: Key Analysis Population Sets

	Number of Subjects (Phase)
All Leukapheresed Population / Full Analysis Set	71 (All Phase 2)
Primary Efficacy Population*	54 (All Phase 2)
Safety Analysis Set	78 (55 subjects in Phase 2 and 23 subjects in Phase 1)

Source: FDA Analysis
*The Applicant's efficacy analysis set included 55 subjects

In ZUMA-3 Phase 2, Fourteen subjects received neither lymphodepleting chemotherapy nor KTE-X19 after leukapheresis, as follows:

- Seven subjects were not treated due to AEs:
  - One subject experienced various AEs following leukapheresis, including tumor lysis syndrome, lung infection, urinary tract infection, and sepsis. The subject died of sepsis
  - One subject's product was not successfully manufactured from the initial leukapheresis material. Following the second leukapheresis, the subject developed a lung infection and respiratory failure and died of PD before they could be treated with KTE-X19.
  - One subject's product was not successfully manufactured from the initial leukapheresis material. The subject developed fungal pneumonia and sepsis shortly after leukapheresis and ultimately died of PD without

undergoing a second leukapheresis.
    - One subject experienced an AE of deep vein thrombosis following leukapheresis, rendering this subject ineligible for the study.
    - One subject experienced various AEs following leukapheresis, including splenic rupture, neutropenic sepsis, aspiration pneumonia, and encephalopathy. The subject then died of cardiac arrest before they could be treated with KTE-X19.
    - One subject experienced various AEs following leukapheresis, including Clostridium difficile infection, septic shock, colitis infection, and myositis. The subject was removed from study per the investigator's decision.
    - One subject developed a hemiparesis due to air embolism following leukapheresis, rendering this subject ineligible for the study. The subject was subsequently treated under a compassionate use protocol.
- Three subjects were identified as not meeting eligibility criteria after leukapheresis:
    - Two subjects were found to have CD19− blasts (both subjects had received prior blinatumomab). For one of these subjects, product was not successfully manufactured from the initial leukapheresis material.
    - One subject was found to have < 5% blasts.
- Four subjects were not treated due to manufacturing failures

In summary, KTE-X19 was successfully manufactured for 65 of 71 subjects (92%) in the full analysis set of Phase 2; thus, the overall manufacturing failure rate was 8% (6 of 71).

Of the 57 subjects who received lymphodepleting chemotherapy, 55 subjects received KTE-X19. Two subjects were not treated with KTE-X19 after receiving lymphodepleting chemotherapy:

- One subject experienced AEs of bacteremia and neutropenic fever that precluded further treatment
- One subject deteriorated after lymphodepleting chemotherapy and no longer met eligibility criteria

Of the 55 subjects who received KTE-X19, 51 subjects had received bridging therapy between enrollment and lymphodepleting chemotherapy.

In Zuma-3 Phase 1, a total of 54 subjects were enrolled; of these, 49 subjects (91%) received lymphodepleting chemotherapy. Five subjects received neither lymphodepleting chemotherapy nor KTE-X19 after leukapheresis, as follows:

- Three subjects were not treated due to AEs:
    - One subject experienced various AEs after leukapheresis, including febrile neutropenia that precluded treatment with KTE-X19, and subsequently

died of PD.
    - One subject developed fungal pulmonary nodules after leukapheresis and was started on inotuzumab.
    - One subject developed a subdural hematoma after leukapheresis that precluded treatment with KTE-X19 and subsequently died of PD.
- One subject's product was not successfully manufactured from the initial leukapheresis material. The subject ultimately died of PD
- One subject did not meet eligibility criteria. Following leukapheresis, the subject was found to have CNS abnormalities (brain lesion) and withdrew from the study.

Of the 49 subjects who received lymphodepleting chemotherapy in Phase 1, 45 subjects received KTE-X19. Four subjects were not treated with KTE-X19 after receiving lymphodepleting chemotherapy, as follows:

- Three subjects experienced AEs:
    - One subject experienced various AEs after lymphodepleting chemotherapy, including respiratory failure, bacteremia, and sepsis. The subject died of sepsis before having the opportunity to be treated with KTE-X19.
    - One subject experienced various AEs after lymphodepleting chemotherapy, including renal failure and sepsis. The subject died of sepsis before having the opportunity to be treated with KTE-X19.
    - One subject had a thromboembolic event following leukapheresis, rendering the subject ineligible for the study. The subject was subsequently treated under a compassionate use protocol.
- One subject was not treated due to a study-wide pause in enrollment and treatment that was instituted by the sponsor following the death of another subject in the study from cerebrovascular accident (the reason not treated was reported as "other"). The subject was started on blinatumomab as salvage chemotherapy.

KTE-X19 was successfully manufactured for 53 of 54 subjects (98%) in the full analysis set of Phase 1.

Of the 45 subjects who received KTE-X19, 43 subjects had received bridging therapy between enrollment and lymphodepleting chemotherapy.

For subjects treated in Phase 1, the median actual follow-up time from the KTE-X19 infusion was 11.4 months (range: 0.2 to 51.7 months), and the median potential follow-up time from the KTE-X19 infusion was 39.4 months (range: 24.4 to 53.5 months); all subjects had ≥ 24 months of potential follow-up.

Disposition of subjects in the safety analysis set

Table 7 summarizes subjects' disposition for the safety analysis set. Overall, 41% of subjects died, 5% withdrew consent and 1% was lost to follow up.

Table 7 FDA - ZUMA-3: Subject Disposition in the Safety Analysis Set

Subject Disposition	Phase 1 N = 23 n (%)	Phase 2 N = 55 n (%)	Overall N = 78 n (%)
Reason for Discontinuation from Study			
Death	12 (52)	20 (36)	32 (41)
Full Consent Withdraw	1 (4.3)	3 (5)	4 (5)
Lost to Follow-up	1 (4.3)	0	1 (1.3)

Source: FDA Analysis. ADSLFDA

Protocol Violations/Deviations

Data:

Important protocol deviations (IPDs) were documented during monitoring visits. In the safety analysis set of Phase 2, IPDs were reported for 18 subjects (33%); of these, 2 subjects (4%) had COVID-19-related IPDs. Each category of IPD occurred in < 10% of subjects. The most frequent IPD was missed bone marrow aspirate (5 subjects, 9%), of which 1 was due to COVID-19 (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 8.6; ADSL, ADDV, ADXV).

The Applicant's Position:

Overall, the IPDs were considered to not impact the overall quality of the data and interpretation of the results.

The FDA's Assessment:

IPDs in the efficacy analysis population included:

- Missing bone marrow (BM) morphological disease assessment prior to leukapheresis in one subject who was a nonresponder
- Missing BM Assessments in five subjects
- Missing laboratory assessments in four subjects
- Missing EMD scans in one subject
- Administration error in one subject (The investigational product was not stored correctly, and filtered tubes were used for administration)

Reviewer comment: *The Reviewer agrees that the IPDs did not impact the interpretation of study results as all missed disease assessments were assessed by the central assessor as non-evaluable disease responses.*

The Reviewer recommended that BIMO inspect the two clinical sites with the most IPDs.

Demographic Characteristics

Data:
Demographic data for ZUMA-3 Phase 2 are summarized in Table 8. Among the 55 subjects who received KTE-X19, the median age was 40.0 years (range: 19 to 84 years), and 8 subjects (15%) were ≥ 65 years of age. Thirty-three subjects (60%) were male, and the majority were white (37 subjects, 67%). Forty-one subjects (75%) were enrolled in the US, and 14 subjects (25%) were enrolled in the EU.

Table 8 Kite - ZUMA-3: Subject Demographics (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
Age (years)	
n	55
Mean (STDEV)	42.2 (16.1)
Median	40.0
Min, Max	19, 84
Age category, n (%)	
< 65 Years	47 (85)
≥ 65 Years	8 (15)
Sex, n (%)	
Male	33 (60)
Female	22 (40)
Ethnicity, n (%)	
Hispanic or Latino	11 (20)
Not Hispanic or Latino	42 (76)
Missing	2 (4)
Race, n (%)	
American Indian or Alaska Native	1 (2)
Asian	3 (5)
Black or African American	1 (2)
White	37 (67)
Other	9 (16)
Missing	4 (7)

	Phase 2 (N = 55)
Country of enrolled sites, n (%)	
Germany	3 (5)
France	10 (18)
Netherlands	1 (2)
United States	41 (75)

Data cutoff date = 09SEP2020.
Abbreviations: Max, maximum; Min, minimum; STDEV, standard deviation.
Note: Percentages are based on the number of subjects treated with any dose of KTE-X19.
Source: m5.3.5.2, ZUMA-3 Primary Analysis CSR, Table 11; ADSL

The FDA's Assessment:

In addition to the Applicant's table of demographics listed above, demographic characteristics displayed in Table 9 include those for the 54 subjects who were included in FDA's primary efficacy analysis and the 71 subjects who were leukapheresed. These are the two populations likely to provide the most useful information to prescribers, and as such are the two populations for which disease response results will be included in the product label. See Section 8.2.4 regarding demographics of the safety analysis set.

The 54 subjects included in FDA's primary efficacy analysis had a median age of 40 years (range 19-84) and were primarily white, non-Hispanic or Latino individuals treated in the United States. The cohort included more men than women.

In efficacy population set (N=54), the median potential follow-up time from KTE-X19 infusion was 16.3 months (range: 10.3, 22.1) and the median actual follow-up time was 12.3 months (range: 0.3, 22.1). In the leukapheresed population (N=71), the median potential follow-up time from leukapheresis date was 17.5 months (range: 13.0, 23.3) and the median actual follow-up time was 12.7 months (range: 0.7, 23.3).

Reviewer comment: *Displaying data from the primary efficacy analysis population and the cohort of all leukapheresed subjects side by side facilitates comparison and demonstrates that the subjects included in FDA's primary efficacy analysis were demographically similar to all subjects enrolled. Demographic features were also similar to those of the 55 subjects included in the Applicant's primary efficacy analysis.*

Overall, the study population appears representative of those with ALL in the US: median age in the 40s, slight predominance in men over women, and a predominance of Caucasians. These are the expected observations for age, sex, and racial distribution.

Table 9 FDA - ZUMA-3: Demographic Characteristics in the Efficacy Population

Demographic Group	Primary Efficacy Analysis N = 54 n (%)	All Leukapheresed N = 71 n (%)
Age		
< 65	46 (85)	60 (85)
≥ 65	8 (15)	11 (15)
<75	53 (98)	70 (99)
≥ 75	1 (1.9)	1 (1.4)
Mean (SD)	42 (16.2)	44.3 (16.2)
Median (Range)	40 (19–84)	44 (19–84)
Sex		
Male	33 (61)	41 (58)
Female	21 (39)	30 (42)
Race		
White	36 (67)	51 (72)
Other	9 (17)	9 (13)
Missing	4 (7)	4 (6)
Asian	3 (6)	4 (6)
Black or African American	1 (1.9)	2 (2.8)
American Indian or Alaska Native	1 (1.9)	1 (1.4)
Ethnicity		
Not Hispanic or Latino	41 (76)	57 (80)
Hispanic or Latino	11 (20)	12 (17)
Missing	2 (3.7)	2 (2.8)
Country		
USA	41 (76)	52 (73)
France	9 (17)	12 (17)
Germany	3 (6)	5 (7)
Netherland	1 (1.9)	1 (1.4)
Canada	0	1 (1.4)

Source: FDA Analysis. ADSLFDA

Other Baseline Characteristics

Data:
Among the 55 treated subjects in Phase 2, 33% had primary refractory disease, 78% had r/r disease after 2 or more lines of therapy, and 29% had first relapse with first remission lasting ≤ 12 months. Subjects had a median of 2 prior lines of therapy (range: 1 to 8 prior lines); 47% had received 3 or more lines of therapy; 42% had received an allo-SCT; 22% had received inotuzumab; and 45% had received blinatumomab. The median blast percentage at baseline (ie, before lymphodepleting chemotherapy) was 60.0% (range: 0% to 98%), and 73% had M3 bone marrow involvement (> 25% blasts) at baseline (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Table 13; ADSL, ADBASE).

The Applicant's Position:
Overall, ZUMA-3 included a high percentage of heavily pretreated subjects with known high-risk features that are associated with a poor prognosis.

The FDA's Assessment:
See Table 10 below for details of baseline disease characteristics for subjects enrolled in the ZUMA-3 Phase 2 study. M3 bone marrow involvement (> 25% blasts) at baseline was observed in 54 (76%) subjects in all leukapheresed population and in 40 (74%) subjects in FDA's primary efficacy analysis population.

Table 10 FDA - ZUMA-3: Baseline Disease Characteristics in the Efficacy Population

Disease Characteristic	**Primary Efficacy Analysis N = 54 n (%)**	**All Leukapheresed N = 71 n (%)**
Baseline Extramedullary Disease Flag	6 (11)	9 (13)
CNS Involvement at Enrollment		
CNS 1	46 (85)	60 (85)
CNS 2	5 (9)	6 (8)
Missing	3 (6)	5 (7)
CNS Involvement at Baseline*		
CNS 1	54 (100)	69 (97)
CNS 2	0	2 (2.8)
Philadelphia Chromosome	14 (26)	19 (27)
Prior Blinatumomab	25 (46)	33 (46)
Prior Inotuzumab	12 (22)	16 (23)

Disease Characteristic	Primary Efficacy Analysis N = 54 n (%)	All Leukapheresed N = 71 n (%)
Blinatumomab as Last Prior Therapy	12 (22)	13 (18)
Prior autologous SCT	1 (1.8)	3 (4.2)
Relapsed or refractory disease post allogeneic SCT	23 (43)	28 39)
Primary refractory	18 (33)	21 30)
Relapsed or refractory to 2nd or greater line therapy	45 (83)	56 (79)
First relapse with first remission <=12 months	15 (28)	20 (28)
Disease status at enrollment		
Refractory relapse	25 (46)	33 (46)
Primary refractory disease	14 (26)	17 (24)
Second or later untreated relapse	11 (20)	15 (21)
First untreated relapse	4 (7)	6 (8)
Baseline ECOG Disease Status		
0	16 (30)	18 25)
1	38 (70)	53 (75)
Number of Prior Lines of Therapy		
Median (Range)	2(1-8)	2 (1-8)
1	9 (17)	11 (15)
2	19 (35)	25 (35)
≥ 3	26 (48)	35 (49)

Source: FDA Analysis. ADSLFDA, ADBASFDA
*Baseline is defined as post-bridging and prior to conditioning chemotherapy
Abbreviations: ECOG: Eastern Cooperative Oncology Group; SCT: stem cell transplant

Reviewer comment: *The Reviewer noted a discrepancy in the ADBASE dataset regarding prior lines of therapy and prior allo SCT:*

- *The correct number of subjects who had two prior lines of therapy or who had r/r to second or greater line of therapy is 45 subjects. Subjects ID* (b) (6) *had two prior lines of therapy and should have a flag checked for r/r to 2nd or greater line of therapy.*

- *The correct number of subjects who had prior allo SCT and who had r/r disease after allo SCT is 23 subjects, as Subject ID (b) (6) received an autologous SCT as prior therapy but was erroneously marked in the eCRF as having received allo SCT.*

Reviewer comment: *The Reviewer identified one subject (Subject ID (b) (6)) to have had EMD at baseline. The subject was reported by the Applicant to not have EMD. See discussion of FDA's efficacy adjudication described in the Efficacy Results below. The subject was included in the analysis of subjects who had EMD at baseline in Table 10 above.*

There were three subjects who had missing CNS disease status at screening however, these subjects had CNS assessments prior to receiving conditioning chemotherapy, which is acceptable.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
All subjects were treated under the care of a professional healthcare provider in the hospital. In the Phase 2 safety analysis set, all subjects received the planned total dose of cyclophosphamide (900 mg/m^2), and all subjects received within 10% of the planned total dose of fludarabine (75 mg/m^2). The majority of subjects (98%) received within 10% of the planned total dose of KTE-X19 (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.1; ADSL, ADDA, ADEX).

In Phase 2, 75% of subjects were treated with corticosteroids (with or without tocilizumab), 80% were treated with tocilizumab (with or without corticosteroids), 67% were treated with corticosteroids and tocilizumab, 40% were treated with vasopressors, 11% were treated with nonsteroidal immunosuppressive agents other than tocilizumab, and 11% were treated with immunoglobulins. Furthermore, 15% of subjects had an endotracheal intubation, and 9% of subjects received mechanical ventilation (m5.3.5.2, ZUMA-3 Primary Analysis CSR Section 11.6; ADSL, ADCM, ADPR).

The Applicant's Position:
No treatment compliance issues were identified. Medical interventions and supportive care were administered per toxicity management guidelines and standard of care.

The FDA's Assessment:
There were two subjects who received KTE-X19 dose within 10% of the planned dose of 1 x 10^6 anti-CD19 CAR T cells/kg (Subject ID (b) (6) One additional subject (ID (b) (6)) from the EU who weighed > 100 kg received a flat dose of 0.81 x 10^8 anti-CD19 CAR T cells, rather than the planned flat dose of 1 x 10^8 anti-CD19 CAR T cells per protocol. This subject's manufactured product was out of

specification (OOS); however, the subject was treated with the OOS dose per the treating investigator's request.

Reviewer comment: *FDA decided to include Subject* (b) (6) *in the efficacy evaluable population, because the subject received a dose within 20% of the planned KTE-X19 dose and no other OOS was observed for this product.*

Medications of interest were considered concomitant if they were administered on or after the KTE-X19 infusion date but before the hospital discharge date (except for immunoglobulins, which were included regardless of whether they were administered before or after the hospital discharge date). Most common concomitant mediations used included: antipyretics (92% of subjects), tocilizumab, intravenous fluids, levetiracetam, ondansetron, dexamethasone, allopurinol, acyclovir, filgrastim, antibiotics and antifungals. These medications were administered either as prophylaxis or to treat AEs.

For details regarding concomitant medication or procedures used to treat AESI (including endotracheal intubation and subjects receiving mechanical ventilation), refer to Section 8.2.4.

Manufacturing time:
KTE-X19 was manufactured in the US. Among the 54 efficacy evaluable subjects, the median time from leukapheresis to product delivery to the treatment site was (b) (4) days (range: (b) (4) days) and the median time from leukapheresis to kTE-X19 infusion was (b) (4) days (range: (b) (4) days).

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The primary efficacy analysis was conducted when the overall study enrollment was complete and 55 subjects treated at the 1.0 x 10^6 anti-CD19 CAR T cells/kg dose level in the Phase 2 mITT analysis set had had the opportunity to be followed for at least 10 months after the KTE-X19 infusion. Additional details are in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 9.1.

In the Phase 2 mITT analysis set, the primary endpoint OCR (CR + CRi) rate per central assessment was 70.9% (95% confidence interval [CI]: 57%, 82%), with a CR rate of 56.4% (95% CI: 42%, 70%). Because the OCR rate was significantly greater ($p < 0.0001$) than the prespecified historical control rate of 40%, the primary efficacy endpoint of ZUMA-3 was met.

In the Phase 2 full analysis set (comprising all subjects who underwent leukapheresis), the OCR (CR + CRi) rate was 54.9% (95% CI: 43%, 67%), with a CR rate of 43.7% (95% CI: 32%, 56%). The OCR rate of 54.9% in the full analysis set was greater than the prespecified historical control rate of 40% (nominal p = 0.0077) (Table 11).

Table 11 Kite - ZUMA-3 Primary and Secondary Efficacy Endpoint Results per Central Assessment (Phase 2)

	mITT Analysis Set (N = 55)	Full Analysis Set (N = 71)
OCR (CR + CRi) rate (95% CI)	70.9% (57%, 82%)	54.9% (43%, 67%)
p-value of exact test for OCR rate ≤ 40%	< 0.0001	0.0077[a]
CR rate (95% CI)	56.4% (42%, 70%)	43.7% (32%, 56%)
MRD-negative rate overall[b,c] (95% CI)	76% (63%, 87%)	-
p-value of exact test for MRD-negativity rate ≤ 30%	< 0.0001	-
MRD-negative rate among OCR (CR or CRi) subjects[b,d] (95% CI)	97% (87%, 100%)	-
KM median (95% CI) DOR[e] (months)	12.8 (8.7, NE)	12.8 (8.7, NE)
KM median (95% CI) OS[f] (months)	18.2 (15.9, NE)	19.2 (10.4, NE)
KM median (95% CI) RFS[g] (months)	11.6 (2.7, 15.5)	7.0 (0.0, 13.2)

Data cutoff date = 09Sep2020.

Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; KM, Kaplan-Meier; mITT, modified intent-to-treat; MRD, minimal residual disease; NE, not estimable; OCR, overall complete remission; OS, overall survival; RFS, relapse-free survival; SCT, stem cell transplant; TKI, tyrosine kinase inhibitor.

Note: 95% CIs are based on the Clopper-Pearson method.

a Nominal p value.

b MRD status is determined by the central laboratory. Numerators for MRD negative rate are based on an MRD-negative finding at any postinfusion visit.

c Percentage is based on the number of subjects in the mITT analysis set.

d Percentage is based on the number of subjects with OCR (CR or CRi). Disease response is based on central assessment.

e DOR is defined as the time from the first complete remission (CR or CRi) to relapse or death from any cause in the absence of documented relapse. Subjects not meeting the criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the data cutoff date, new anticancer therapy (excluding resumption of a TKI) start date, or SCT date, whichever was earlier.

f OS for the mITT analysis set is defined as the time from the KTE-X19 infusion date to the date of death from any cause. OS for the full analysis set is defined as the time from the enrollment date to the date of death from any cause.

g RFS for the mITT analysis set is defined as the time from the KTE-X19 infusion date to the date of relapse or death from any cause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response were counted as events on the KTE-X19 infusion date. RFS for the full analysis set is defined as the time from the enrollment date to the date of relapse or death from any cause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response and subjects who were enrolled but not dosed were counted as events on the enrollment date.

Source: m5.3.5.2, ZUMA-3 Primary Analysis CSR, Table 42; ADSL, ADEFF, ADTTE, ADMI.

OCR rate was examined in subgroups defined by demographic, baseline disease, and treatment characteristics. Across most evaluable subgroups, OCR rates ranged from 42% to 100%; these rates were generally consistent with the OCR rate of 70.9% observed for all subjects (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Figure 6; ADSL, ADBASE, ADEFF).

The Applicant's Position:

The response rates achieved in ZUMA-3 compare favorably to those observed in the Phase 3 TOWER study, which compared blinatumomab to standard-of-care chemotherapy {Kantarjian 2017} and used the same stringent hematologic recovery criteria for OCR as used in ZUMA-3. The pooled estimate of OCR rate in the TOWER study was 32%. By contrast, ZUMA-3 demonstrated an OCR rate of 70.9% in the mITT analysis set of Phase 2.

The response rates for KTE-X19 in ZUMA-3 are especially notable considering that the subject population was heavily pretreated; 45% of subjects had previously received blinatumomab, 22% had previously received inotuzumab, and 42% had previously received an allo-SCT, with many subjects receiving double or triple combinations of these therapies. Furthermore, 73% of subjects had high disease burden at baseline, defined as M3 bone marrow involvement (> 25% blasts), which is usually associated with poor efficacy outcomes {Kantarjian 2017, Park 2018}.

A total of 15% of subjects in the mITT analysis set were ≥ 65 years of age; these subjects had an OCR rate of 100% following KTE-X19 treatment. Thus, KTE-X19 offers a new treatment option to elderly patients, who currently have limited options and often experience poor outcomes with intensive chemotherapy or SCT {Aldoss 2019}.

The FDA's Assessment:

Schedule of Efficacy Assessments

Subjects were to be evaluated for disease response by the site investigator at the times indicated in the schedule of assessments (Table 49 and Table 50 in Appendix Section 16.3). First disease assessment occurred on Day 28, followed by Week 8, Month 3, and every 3 months until Month 24. Disease response was evaluated by the investigator using the overall disease response classification as shown in Table 51 and Table 52 (Section 17.4) and included bone marrow evaluations, as well as imaging for subjects with known non-CNS extramedullary disease at baseline.

All subjects in Phase 2 were also to be evaluated for disease response by an independent review committee (central assessment). The central assessment of disease response used the same overall disease response classification, with the exception that

an overall disease response of CR, CRi, or CRh was to be adjusted for a more conservative assessment if platelet transfusion or filgrastim had been administered within 7 days before the disease assessment.

Reviewer comment: *To facilitate FDA's review, the Applicant submitted in response to IR received on 24 May 2021 under eSeq 0101, a summary table (in Excel format titled "Phase 2 Subjects who received platelets or G-CSF up to 7 days prior to disease assessment"). The table identified all subjects from Phase 2 who received platelets or filgrastim up to 7 days prior to any disease assessment and their corresponding overall disease assessment made by the independent reader.*

Efficacy evaluable population

The efficacy evaluable population consisted of 54 subjects who were enrolled and treated in ZUMA-3 Phase 2 study and who had documented disease at baseline post-bridging therapy. FDA efficacy evaluable population excluded one subject (Subject ID (b) (6)) from that of the Applicant's (N=55) because the subject lacked presence of BM blasts at baseline disease assessment post-bridging chemotherapy. Subject ID (b) (6) presented at time of screening with 89% BM blasts and 82% circulating blasts. Bridging chemotherapy consisted of methotrexate (1000 mg/m^2), Cytarabine (12 g/m^2), dexamethasone, and ponatinib, which ended 24 days prior to dosing of KTE-X19. Post-bridging BM assessment after bridging therapy indicated 0% blasts.

Reviewer comment: *The Reviewer considered the bridging therapy that the subject received to have possibly contributed to the efficacy seen post KTE-X19 infusion; and therefore, the contribution of KTE-X19 cannot be fully assessed. Therefore, this subject was considered non-evaluable. However, note that this subject achieved CR and thus will be considered a responder when calculating the response rate for all leukaphersed subjects (i.e., ITT population).*

Three additional subjects were identified who did not have documented blasts in the BM post-bridging therapy (IDs (b) (6) *). However, the Applicant submitted additional information to confirm that the subjects had increase BM blasts based on local bone marrow biopsies or central assessment of the biopsy samples. All three subjects had received low intensity bridging therapy (e.g., 1-2 doses of vincristine). These three subjects were included in the efficacy evaluable population.*

Definition of CR

The definition of response per protocol encompasses BM blasts ≤5%; However, the Review team disagrees with the Applicant's definition. The Review team does not consider BM blasts =5% to be a clinically meaningful response. A clinically meaningful response should include BM blasts of <5% (rather than ≤5%).

Reviewer comment: *The Applicant clarified in response to IR that in ZUMA-3 Phase 2, following KTE-X19 infusion, there were no instances in which the percentage of BM blasts was "=5%.". In the LB domain, the percentage of Blasts (LBTESTCD = PCTBLAST) were recorded as '<5' in several cases. In these instances, LBORRES (Original result) and LBSTRESC (Standard result) were populated with the character value recorded, i.e., '<5', but the numeric value LBSTRESN (Standard Numeric result) was assigned as 5, as the symbol '<', cannot be included in the Numeric result (LBSTRESN).*

Primary Endpoint: Best overall response (BOR)

FDA adjudication of BOR

Based on review of all data, the Reviewer downgraded three responses to nonresponders and one CR to CRi. See details below and summary in Table 12.

- Subject ID (b) (6) :
  - Best overall response is no response. Based on review of additional information and imaging reports submitted by the Applicant in response to several IRs, the subject was identified by the Reviewer to have evidence of extramedullary disease (EMD) at enrollment (splenomegaly and presence of several osseous lesions) which was not reported by the Applicant. There was no evidence of spleen normalization and disappearance of osseous lesions despite the subject achieving hematologic and morphologic CR.

- Subject ID (b) (6)
  - BOR is BFBM (not CRi) due to receiving filgrastim (from Day 8 to Day 59). Subject had no platelet recovery and received Allo SCT on Day 133; Therefore Day 178 could not be CRi and disease assessment for Day 28 and Day 59 is BFBM.

- Subject ID (b) (6)
  - BOR is BFBM on Day 38. Day 62 disease response is "Relapse" due to EMD (not CRi). This is based on the Readjudication of Radiologists reads

(which occurred on 6/14/2021 per the Applicant's request): Radiologist#1 indicated a disease assessment of PD (based on large spleen and no spleen visualization on prior imaging). Radiologist# 2: indicated CR (based on target and non-target (NT) cervical lymph nodes). The Adjudicator reconsidered the CR that was initially assigned. The subject started new therapy on Day 104.

- Subject ID (b) (6)
  - BOR is CR on Day 56 (not on Day 31) due to receiving filgrastim. Day 31 disease response is CRi due to administration of filgrastim PRN, and CR on Day 56.

Table 12 FDA - ZUMA-3: FDA Adjudication of Best Overall Responses in Phase 2

Subject ID	Applicant's BOR	FDA Adjudication of BOR
Changed to nonresponders	Responder	
(b) (6)	CR on Day 97	No response (EMD)
(b) (6)	CRi on Day 59	No response (BFBM on Day 28 and Day 59)
(b) (6)	CRi on Day 62	No response (BFBM on Day 38)
Remained a responder		
(b) (6)	CR on Day 31	CR Day 56

Source: FDA Analysis
Abbreviations: BOR: best overall response; EMD: extramedullary disease; BFBM: blast free bone marrow

Efficacy Results: BOR

The primary objective of ZUMA-3 was to evaluate the efficacy of KTE-X19 in subjects with r/r B-ALL by measuring the primary endpoint of OCR as assessed centrally. Baseline disease and disease responses were assessed both by the site investigator and by the central assessor. Results of the primary endpoint analysis are shown in Table 13. All 95% CIs were calculated by the Clopper-Pearson method. In the primary efficacy population, OCR was observed in 35 (65%) subjects and CR rate was observed in 29 (54%) subjects. No subject achieved a BOR of CRh. Six subjects achieved BFBM, seven subjects had no response, three subjects relapsed, and three subjects were not evaluable.

Table 13 FDA - ZUMA-3: Primary Efficacy Endpoint per Protocol - Best Overall Response per FDA Adjudication

Best Overall Response	Primary Efficacy Analysis (N = 54)	All Leukapheresed (N = 71)
OCR (CR + CRi) rate n (%) (95% CI)	35 (64.8%) (50.6%, 77.3%)	36* (50.7%) (38.5%, 62.7%)
CR rate n (%) (95% CI)	29 (53.7%) (39.6%, 67.3%)	30* (42.2%) (30.6%, 54.5%)
CRi rate n (%) (95% CI)	6 (11.1%) (4.1%, 22.6%)	6 (8.4%) (3.1%, 17.4%)

Source: FDA Analysis. ADEFFFDA
*Includes Subject ID (b) (6) response
Abbreviation: OCR: Overall complete response rate; CR: complete response; CRi: complete response with incomplete hematologic recovery

Reviewer comment: *As displayed in Table 13, the CR+CRi rate after treatment with KTE-X19 in ZUMA-3 was not changed substantially by FDA's adjudication, which resulted in exclusion of one subject from the primary efficacy population and reclassification of disease response from responders to nonresponders for three subjects.*

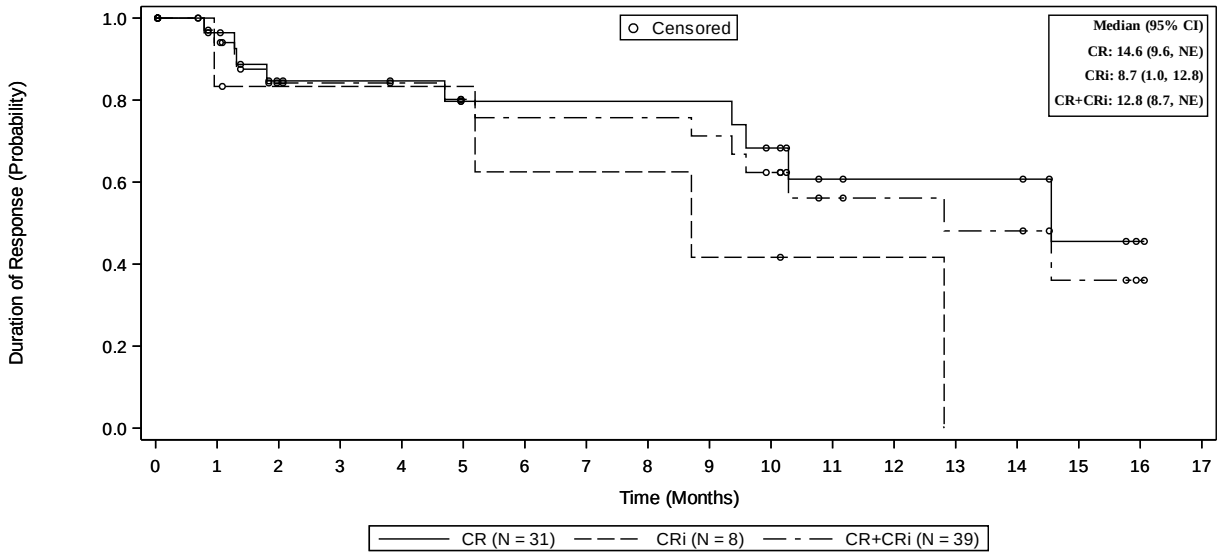
Efficacy Results – Secondary and other relevant endpoints

Data:

The overall MRD^- rate, as determined by the central laboratory, was 76% (95% CI: 63%, 87%), which was significantly greater ($p < 0.0001$) than the prespecified control rate of 30%. Therefore, the secondary efficacy endpoint of ZUMA-3 was met. Among subjects with CR or CRi, the MRD^- rate was 97% (95% CI: 87%, 100%) (Table 11). Additional details are provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 9.1.1.2.1; ADSL, ADEFF, ADMI.

Among the 39 subjects in the mITT analysis set who achieved a CR or CRi, the Kaplan-Meier (KM) median DOR was 12.8 months (Table 11), with a reverse KM median follow-up time for DOR of 10.2 months. By response subgroup, the KM median DOR was 14.6 months for subjects with CR and 8.7 months for subjects with CRi (Figure 2).
A sensitivity analysis was conducted in which disease assessments obtained after allo-SCT were included in the derivation of DOR. In this analysis, the KM median DOR was 12.8 months, consistent with the main analysis. Additional details are provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 9.1.1.2.3; ADSL, ADEFF, ADTTE.

Figure 2 Kite - KM Plot of DOR by Best Overall Response Groups per Central Assessment (Phase 2, mITT Analysis Set: Subjects With a CR or CRi)

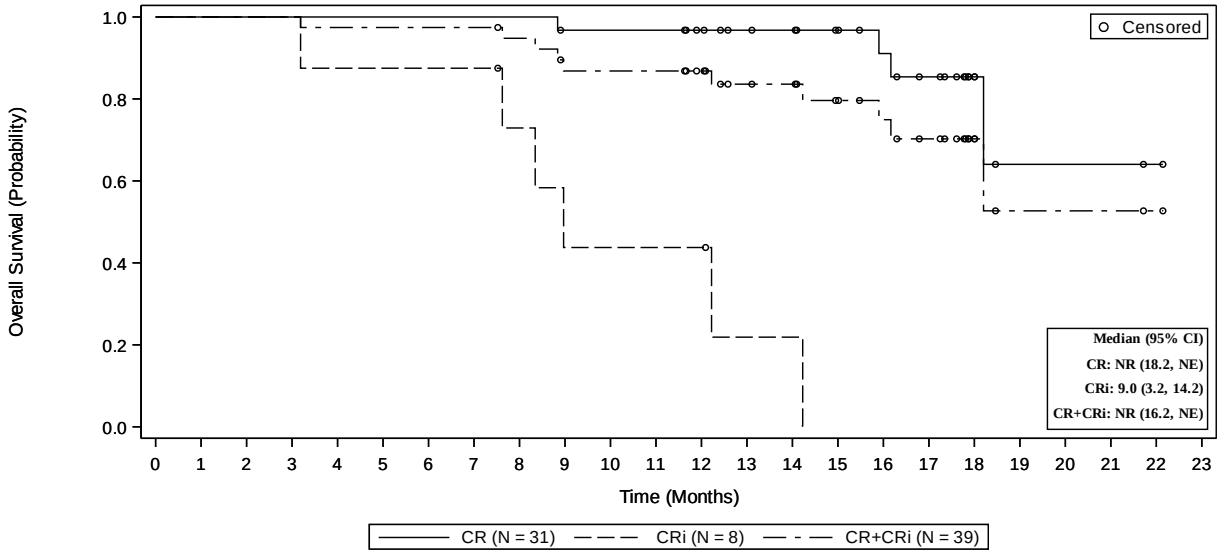


CR at risk	31	26	19	18	17	14	14	14	14	14	11	7	6	6	6	3	1	0
(CR censored)	(0)	(4)	(8)	(9)	(10)	(12)	(12)	(12)	(12)	(12)	(13)	(16)	(17)	(17)	(17)	(19)	(21)	(22)
CRi at risk	8	5	4	4	4	4	3	3	3	2	2	1	1	0	0	0	0	0
(CRi censored)	(0)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
CR+CRi at risk	39	31	23	22	21	18	17	17	17	16	13	8	7	6	6	3	1	0
(CR+CRi censored)	(0)	(6)	(11)	(12)	(13)	(15)	(15)	(15)	(15)	(15)	(16)	(20)	(21)	(21)	(21)	(23)	(25)	(26)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; KM, Kaplan Meier; mITT, modified intent to treat; NE, not estimable.
Source: m5.3.5.2, ZUMA-3 Primary Analysis CSR, Figure 8; ADSL, ADEFF, ADTTE.

For the 55 subjects in the Phase 2 mITT analysis set, the KM median OS was 18.2 months (Table 11). The KM median OS was not reached for subjects with CR and was 9.0 months for subjects with CRi (Figure 3) (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 9.1.1.2.5; ADSL, ADTTE).

Figure 3 Kite - KM Plot of OS: CR vs CRi (Phase 2, mITT Analysis Set: Subjects with a CR or CRi)

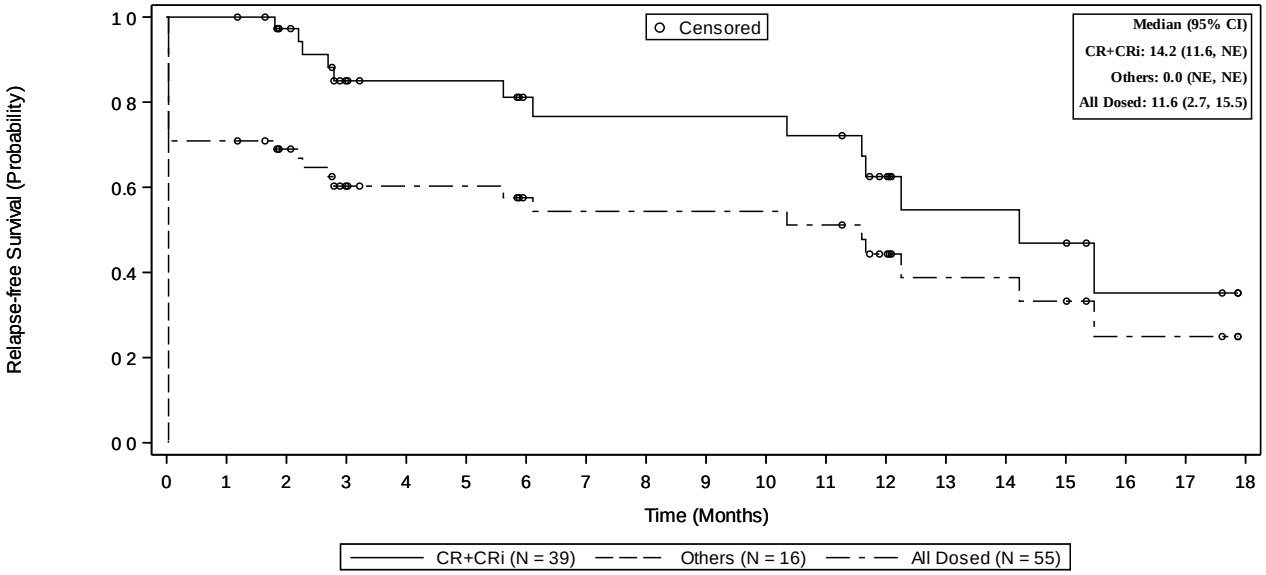


CR at risk	31	31	31	31	31	31	31	31	31	29	29	29	26	23	22	19	16	13	6	2	2	2	1	0
(CR censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(4)	(7)	(8)	(11)	(13)	(15)	(22)	(25)	(25)	(25)	(26)	(27)
CRi at risk	8	8	8	8	7	7	7	7	5	3	3	3	3	1	1	0	0	0	0	0	0	0	0	0
(CRi censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)
CR+CRi at risk	39	39	39	39	38	38	38	38	36	32	32	32	29	24	23	19	16	13	6	2	2	2	1	0
(CR+CRi censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(2)	(2)	(5)	(9)	(10)	(13)	(15)	(17)	(24)	(27)	(27)	(27)	(28)	(29)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan Meier; mITT, modified intent to treat; NE, not estimable; NR, not reached; OS, overall survival.
Source: m5.3.5.2, ZUMA-3 Primary Analysis CSR, Figure 10; ADSL, ADTTE, ADEFF.

For the 55 subjects in the Phase 2 mITT analysis set, the KM median RFS was 11.6 months (Table 11). Among subjects with CR or CRi, the KM median RFS was 14.2 months (Figure 4). A sensitivity analysis was conducted in which disease assessments obtained after allo-SCT were included in the derivation of RFS. In this analysis, the KM median RFS was 11.6 months, consistent with the main analysis (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 9.1.1.2.6; ADSL, ADTTE).

Figure 4 Kite - KM Plot of RFS per Central Assessment: Subjects with a CR or CRi vs Others (Phase 2, mITT Analysis Set)



CR+CRi at risk	39	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0
(CR+CRi censored)	(0)	(0)	(5)	(10)	(12)	(12)	(15)	(15)	(15)	(15)	(15)	(15)	(18)	(21)	(21)	(21)	(23)	(23)	(26)
Others at risk	16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(Others censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
All Dosed at risk	55	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0
(All Dosed censored)	(0)	(0)	(5)	(10)	(12)	(12)	(15)	(15)	(15)	(15)	(15)	(15)	(18)	(21)	(21)	(21)	(23)	(23)	(26)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan Meier; mITT, modified intent to treat; NE, not estimable; NR, not reached; RFS, relapse free survival.
Source: m5.3.5.2, ZUMA-3 Primary Analysis CSR, Figure 12; ADSL, ADTTE, ADEFF.

The Applicant's Position:

Among subjects who achieved a CR or CRi, the KM median DOR was 12.8 months, with a KM median DOR of 14.6 months for subjects with CR. Ten of 55 subjects (18%) in the mITT analysis set received allo-SCT while in remission after the initial KTE-X19 infusion. Notably, the median DOR was similar when subjects were censored (main analysis) or were not censored (sensitivity analysis) at the time of allo-SCT. The median OS was 18.2 months in the ZUMA-3 Phase 2 mITT analysis set, compared with the median OS of 6.9 months in the meta-analysis.

The FDA's Assessment:

Duration of Response

DOR Definition
Per the SAP, DOR was derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy and allo SCT (excluding resumption of TKIs). The DOR for subjects who underwent allo SCT while in remission was censored at the last evaluable disease assessment prior to the allo SCT; the DOR for subjects who underwent other new anticancer therapies in the absence of documented relapse was censored at the last evaluable disease assessment prior to the new anti-cancer therapies.

For subjects with Ph+ ALL, all TKIs, including, but not limited to, imatinib, dasatinib, and ponatinib, were to be stopped at least 1 week prior to KTE-X19 infusion. In subjects who achieved CR, a TKI could be resumed 2 months after KTE-X19 infusion at the investigator discretion.

FDA adjudication of efficacy for DOR
Based on review of the submitted data (in the initial sBLA submission and in response to IRs), the Reviewer readjudicated the responses and DOR for several subjects, the majority of which was because of receiving filgrastim or platelets transfusion up to 7 days prior to disease assessments. See details below and summary in Table 14.

- Subject ID (b) (6):
  - Date of relapse is Day 181 (which is the date of BM relapse) not Day 185 as reported by the Applicant (which is the date of the independent assessor's disease assessment).
- Subject ID (b) (6):
  - 1st response should be CR on Day 62
  - Response on Day 28 should not be CRi, due to receiving platelet transfusion on Day 22 "within 6 days prior to disease assessment" and receiving filgrastim on Day 26 "within 2 days prior to disease assessment". Therefore, Day 28 should be BFBM
- Subject ID (b) (6)
  - Had BOR of CRi on Day 28. The subject had missing bone marrow assessments on Week 8 and Month 3 (and no other disease assessments afterwards). The Applicant clarified in response to IRs that this subject partially withdrew consent on Day 192. The last adequate disease assessment available for this subject is from Day 28. The subject died due

to PD on an unknown date. Per protocol, the Applicant considered the date of death as the event date (rather than the date of PD). However, since the subject had long period of missing disease assessments, this subject was considered by FDA to be "lost to follow up" and therefore the subject should be censored using the last adequate disease assessment (on Day 28) as the censoring date. Note that because the updated ADTTEFDA dataset was already submitted at the time of the reviewer of this case, the Reviewer didn't ask the Applicant to resubmit the dataset to reflect this change. The dataset continues to list this subject as having an event on the date of death.

- Subject ID (b) (6)
  - 1st response should be CR on Day 62 (not CRi on Day 31).
  - Day 31 response should be BFBM (given that the subject received filgrastim from Day 18 to Day 49 and Platelets were 61 on Day 31)
- Subject ID (b) (6) :
  - 1st response should be CR on Day 56 (not CRi on Day 28).
  - Day 28 ANC was 2670 and platelets were 67. The subject received filgrastim on Day 1 to Day 25 and on Day 27. Therefore, the first overall disease assessment should be BFBM.

Table 14 FDA - ZUMA-3: FDA Adjudication of Duration of Response in the Primary Efficacy Population

Subject ID	Applicant's Response	FDA Adjudication of Response
(b) (6)	Relapse on Day 185	Relapse on Day 181
(b) (6)	First response (CRi) on Day 28	First response (CR) on Day 62
(b) (6)	Event date was the date of death (Day 432)	Subject censored on Day 28 (Date of last adequate disease assessment)
(b) (6)	First response (CRi) on Day 31	First response (CR) on Day 62
(b) (6)	First response (CRi) on Day 28	First response (CR) on Day 56

Source: FDA Analysis

Efficacy results: Key Secondary Endpoint: DOR

DOR in the primary efficacy population per FDA's adjudication is provided in Table 15 and plotted in Figure 5. Estimated median DOR was 13.6 months (95% CI: 9.4, NE). Censoring rate was 69% and median follow-up was 5 months.

Outcomes are shown for all responders, and according to BOR of CR or CRi. Rates of continued remission are shown as Kaplan-Meier estimates; however, due to the maturity of the data, the 12-month estimates may be unstable.

Table 15 FDA - ZUMA-3: Duration of Response in the Primary Efficacy Population

	Primary Efficacy Population (phase 2) (N=54)
Number of responders	35
Duration of response (months) Estimated median (95% CI)	13.6 (9.4, NE)
Median follow-up time (min, max)	5.0 (0.03+, 16.07+)
Percentage censored	69%
Remain in remission	12 (34%)
Allogeneic SCT	8 (23%)
Other new anti-cancer therapy	3 (9%)
Missing > 2 disease assessments	1 (3%)
DOR if BOR is CR (months)	
Estimated median (95% CI)	NE (9.6, NE)
Median follow-up time (min, max)	5.0 (0.03+, 16.07+)
Percentage censored	72%
DOR if BOR is CRi (months)	
Estimated median (95% CI)	6.9 (1.0, NE)
Median follow-up time (min, max)	3.0 (0.03+, 10.2+)
Percentage censored	50%
DOR landmarks (months) % (95% CI) KM estimation	
3- month	82% (62.0, 92.1)
6- month	77% (55.7, 89.2)
9- month	72% (50.0, 86.0)
12- month	55% (31.2, 73.8)

Source: FDA Statistical Reviewer, ADEFFFDA, ADTEEFDA
Abbreviations: CI: confidence interval; DOR: duration of response; NE: not estimable

Reviewer comment: *Among the six subjects with BOR of CRi, three were censored:*

1. *One subject was censored prior to allo SCT (which he underwent on Month 2)*
2. *One subject remained in remission until Day 367 (last disease assessment).*
3. *One subject was censored due to two missing disease assessments. The subjects died later (on Day 432) due to PD however, because of the missing disease assessments, the*

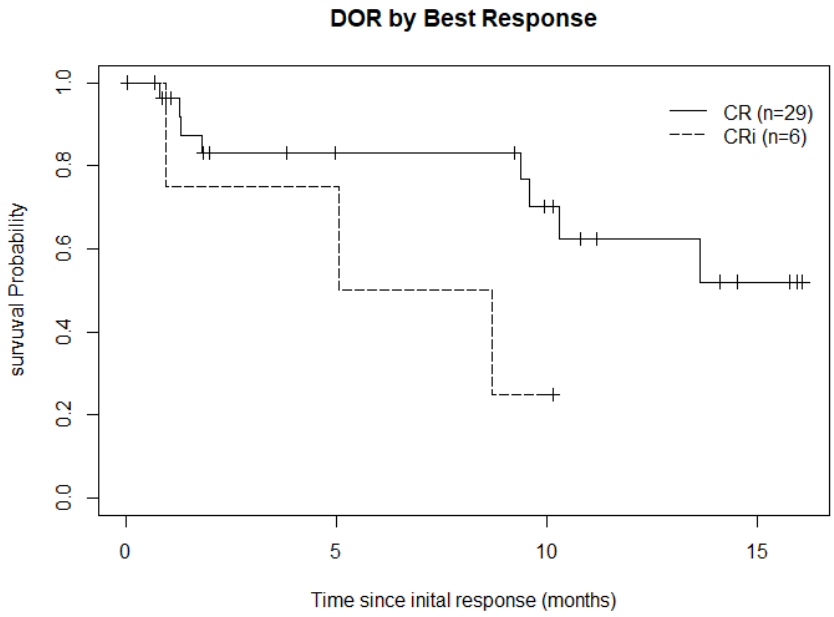
Reviewer didn't consider the death as an event and rather considered the subject as lost to follow-up. The subject was censored at last disease assessment (on Month 1).

Per protocol, subjects with Ph+ ALL who achieved CR, a TKI could be resumed 2 months after KTE-X19 infusion at the investigator's discretion. TKI was to start no earlier than 2 months after achieving CR. Five of the 35 responders in the primary efficacy analysis set received TKI after achieving CR. All were on TKI prior to enrollment on ZUMA-3:

- *Two subjects started TKI after achieving CR*
- *Two subjects started TKI after CR and subsequent relapse*
- *One subject started TKI after achieving CRi (Subject ID* (b) (6) *who had missing BM assessments on Week 8 and Month 3 however, per the investigator's assessment, this subject had a CR at Week 8 and thus was started on TKI*

Because of the small number of subjects who resumed TKI following KTE-X19 treatment, definitive conclusion cannot be made regarding the potential contributary effect of TKI in the observed responses.

Figure 5 FDA - ZUMA-3: Duration of Response by Best Overall Response in the Primary Efficacy Population



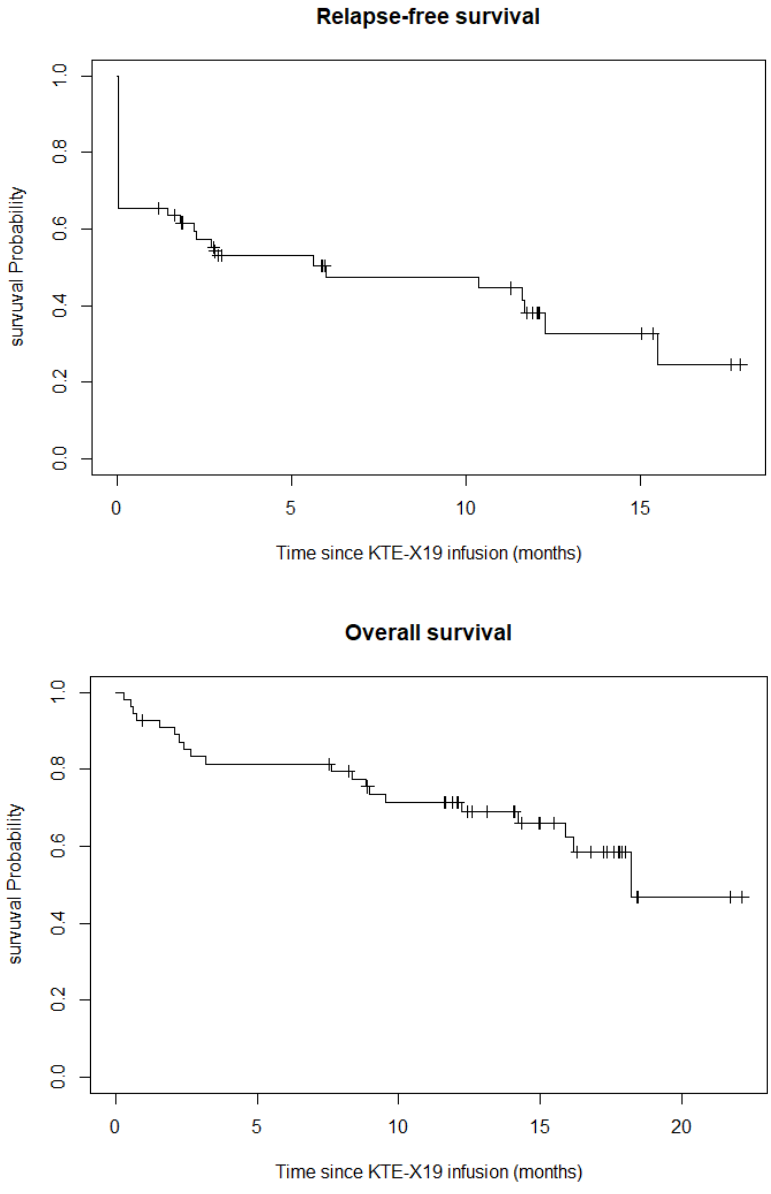
Source: FDA Statistical Reviewer, ADEFFFDA, ADTEEFDA

Reviewer comment: *Responses were more durable in subjects achieving BOR of CR as compared to those with BOR of CRi.*

Progression-Free Survival and Overall Survival

See Figure 6 for FDA's Kaplan-Meier curves of RFS (top panel) and OS (bottom panel) for the primary efficacy analysis population. The estimated median RFS was 6.0 months (95% CI: 1.8, 14.2), and the estimated median OS was 18.2 months (95% CI: 15.9, NE).

Figure 6 FDA - ZUMA-3: Kaplan-Meier Curves for RFS and OS in the Primary Efficacy Population



Source: FDA Statistical Reviewer

Reviewer comment: *Survival data from a single-arm study needs to be interpreted with caution because it cannot be known with certainty what the control results would have been had there been a control group in the study.*

Minimal Residual Disease (MRD)

CDRH provided review of the (b) (4) MRD (b) (4) assay to determine if it is analytically validated for the proposed 10^{-4} cut-off point for r/r ALL. The review team noted that the use of this MRD assay in the context of the current sBLA is as an efficacy endpoint rather than for selection of patients for an investigational clinical trial or for clinical decision-making regarding further therapy.

CDRH concluded that based on the information provided by the Applicant in the initial sBLA submission and in response to IRs, they do not agree that the (b) (4) MRD assay was appropriately validated for the proposed 10^{-4} or for any cut-off point. Because of the lack of appropriate analytical validation, the "(b) (4) MRD assay for B-ALL" would not provide a reliable answer in determining the level of MRD as a secondary efficacy endpoint in the ZUMA-3 study. A summary of CDRH's concerns regarding the assay's analytical reliability is provided below:

- The Applicant is missing multiple analytical validation studies.
- Inappropriate analytical validation study designs were used.
- Inconsistent analytical validation study designs were used between laboratory sites.
- Inappropriate sample selection and usage.
- Absence of appropriate sample stability studies for shipped specimens.
- Sample type commutability studies were not provided.
- CDRH does not recognize the (b) (4) MRD assay as an analytically validated assay.
    - In the materials provided, (b) (4) indicated that they have designed their MRD assay to conform with (b) (4) specifications. However, as CDRH does not presently recognize the (b) (4) MRD assay as an analytically validated assay, claims of conformity to (b) (4) specifications as a surrogate for analytical validation are irrelevant.
- The proposed MRD assay does not conform with the recommendations, regarding the required data for the analytical validation of the MRD assay, contained within the CBER and CDER industry guidance document "*Hematologic malignancies: regulatory considerations for the use of minimal residual disease in development of drug and biological products for treatment"* (January 24, 2020).

- Furthermore, the Applicant has not addressed whether their therapy (i.e. KTE-X19, an anti-CD19 CAR T cell) will affect expression of the target (i.e. CD19) and therefore the detectability of B-ALL MRD cells. As the sponsor proposes to pre-gate on CD19+ B cells to examine their phenotypes, if expression of CD19 is affected the sponsor would not be able to detect it given the current gating scheme. For example, if CD19 expression is lost or a truncated version of CD19 is expressed within B-ALL cells in response to KTE-X19 CAR-T treatment, residual B-ALL cells would not be detected, and the subject would be assessed as MRD-.
- In addition, while it is apparent from the ZUMA-3 schedule of assessments that bone marrow aspirates will be specifically examined for MRD rates as a secondary efficacy endpoint, the intended usage of the "(b) (4) MRD assay for B-ALL" assay includes both bone marrow and peripheral blood samples. If multiple sample matrices are desired as claimed in the Intended Use (i.e. bone marrow AND peripheral blood samples), a complete analytical validation would need to be performed for each intended use matrix. As it appears that peripheral blood will not be examined in the ZUMA-3 MRD schedule of assessments, the least burdensome approach would be to perform all of the analytical validation studies using bone marrow.

Reviewer comment: *Since CDRH's concerns were about the validation of the assay rather than the conduct of the individual testing, there is a possibility that additional information may resolve the validation question and allow the test results to be considered credible, so the Reviewer chose to review the MRD data at this time for use in the future if the validation questions were resolved.*

The Applicant defined the MRD− rate as the incidence of an MRD− response, where MRD− was defined as MRD < 10^{-4} per the standard assessment by (b) (4) performed by the central laboratory. Subjects were considered MRD− overall if they achieved an MRD− response at any post-infusion visit (i.e., Day 28, Week 8, or Month 3). The MRD− rates and 95% CIs were to be estimated for all treated subjects and subjects with a CR, CRi, and either CR or CRi combined. The Applicant's definition was not considered acceptable by the review team. MRD- rate should be defined as MRD negative status at time of achieving CR (not at any time point post product infusion).

Based on FDA's analysis, MRD- rate at time of CR was observed in 24 of 54 subjects (44.4%) (CI: 30.9%, 58.6%).

Reviewer comment: *The following subjects were not considered to have MRD- status:*

- *Subject ID* (b) (6)
    - *Did not have central assessment for MRD on Day 58. MRD was negative*

on Day 28, but the subject had BFBM on Day 28. Subsequently, MRD by Local lab was 4.43% on Day 58.

- *Subject ID* (b) (6)
  - *Achieved CR on Day 177; however, there was no MRD assessment on that day. No further MRD testing was performed. MRD was negative on Day 114, however no CBC was done. Subject achieved CRi on Day 27 and had non-evaluable disease response by the central assessor due to missing BM assessments on Day 58 and Day 86. Because MRD testing was done 63 days prior to day of CR, this MRD negative test was not considered adequate.*
  - *Note that this subject is the one subject who was excluded from the subjects who achieved CR within the first 3 months of KTE-X19 infusion.*
- *Subject ID* (b) (6)
  - *Achieved CR on Day 85. However, MRD was positive on that day. MRD was negative on Day 29 when the subject's disease response was CRh. MRD was also negative on Day 57 when the subject achieved CRi.*
- *Subject ID* (b) (6)
  - *Achieved CR on Day 58. However, MRD was positive on that day. MRD was negative on Day 29 when the subject achieved CRi.*

In addition, Subject (b) (6) *achieved CR on Day 84 however the subject did not have samples sent to the central laboratory for MRD assessment. This subject was not considered to be MRD negative by the Applicant's analysis nor by the Reviewer.*

Durability of Response

Data:
Pharmacokinetic data on the relationship between anti-CD19 CAR T-cell persistence and relevant endpoints are provided in Section Secondary and other relevant endpoints, Table 11, and a KM Plot of DOR is shown in Figure 2.

The FDA's Assessment:
See review of duration of response above.

Efficacy Results – Subpopulations

The FDA's Assessment:

Table 16 shows the subgroup analysis of OCR at any time on study by demographic characteristics of the subjects in the efficacy evaluable set. By geographic region, the

OCR was 49% in the 41 subjects treated in the US and 69% in the 13 subjects treated ex-US. The maximum number of subjects treated at a given site was seven subjects; 18 sites treated 1 or 2 subjects, the rest of sites treated 3, or 4 subjects. Due to the small number of subjects treated at each site, no subgroup by site was performed.

Table 16 FDA - ZUMA-3: OCR by Demographic Characteristic in the Primary Efficacy Population

Subgroup		Subgroup size N	Responders n (%)	95% CI* (%)
Overall	54 (100%)	54	35 (65%)	(51%, 77%)
Age	< 65 years	46	27 (59%)	(43%, 73%)
	≥ 65 years	8	8 (100%)	(63%, 100%)
Sex	Female	21	12 (57%)	(34%, 78%)
	Male	33	23 (70%)	(51%, 84%)
Race	White	36	25 (69%)	(52%, 84%)
	Asian	3	3 (100%)	(29%, 100%)
	Black or African American	1	1 (100%)	(3%, 100%)
	American Indian or Alaska Native	1	1 (100%)	(3%, 100%)
	Other	9	3 (33%)	(7%, 70%)
	Unknown	4	3 (75%)	(19%, 100%)
Ethnicity	Hispanic or Latino	11	5 (45%)	(17%, 77%)
	Not Hispanic or Latino	41	29 (71%)	(54%, 84%)
	Unknown	2	1 (50%)	(1%, 100%)

Source: FDA Statistical Reviewer
*Clopper-Pearson exact confidence interval

Reviewer comment: *Per the Clinical Pharmacology Reviewer; AUC0-28 d was higher in subjects who are 65 years of age or older compared to subjects < 65 years old. However, although efficacy and expansion of KTE-X19 appears to be better for subjects 65 years of age and older compared to those who are younger than 65 years old, there are too few subjects to robustly support any conclusions drawn from evaluations of efficacy among these subjects. OCR otherwise appears to be consistent across race, ethnicity, and sex.*

Table 17 shows the subgroup analysis of OCR at any time on study by other baseline characteristics.

Table 17 FDA - ZUMA-3: OCR by Other Baseline Characteristics in the Primary Efficacy Population

Subgroup		Subgroup size N	Responders n (%)	95% CI* (%)
Overall	54 (100%)	54	35 (65%)	(51%, 77%)
ECOG	0	16	13 (81%)	(54%, 96%)
	1	38	22 (58%)	(41%, 74%)
Prior Allogeneic SCT	N	31	19 (61%)	(42%, 78%)
	Y	23	16 (70%)	(47%, 87%)
No. of Prior Regimen	1	9	6 (67%)	(30%, 93%)
	2	19	11 (58%)	(34%, 80%)
	3	14	9 (64%)	(35%, 87%)
	4	10	7 (70%)	(35%, 93%)
	5	1	1 (100%)	(3%, 100%)
	8	1	1 (100%)	(3%, 100%)
Prior Blinatumomab	N	29	21 (72%)	(53%, 87%)
	Y	25	14 (56%)	(35%, 76%)
Prior Inotuzumab	N	42	27 (64%)	(48%, 78%)
	Y	12	8 (67%)	(35%, 90%)
Disease status at Enrollment	First untreated relapse	4	2 (50%)	(7%, 93%)
	Primary refractory disease	14	9 (64%)	(35%, 87%)
	Refractory relapse	25	17 (68%)	(47%, 85%)
	Second or later untreated relapse	11	7 (64%)	(31%, 89%)

Source: FDA Statistical Reviewer
*Clopper-Pearson exact confidence interval

Review Comment: *OCR appears to also be consistent across baseline characteristics including prior allogeneic HSCT, number of prior regimen, prior inotuzumab and disease status at enrollment. Notably, the point estimate of CR is slightly lower (56%) in subjects who received prior blinatumomab compared to subjects who didn't (72%), however, the CIs overlap due to the small sample size and therefore definitive conclusion may not be made.*

Table 18 shows the subpopulation analysis of CR within 3 months of KTE-X19 infusions.

Table 18 FDA - ZUMA-3: Subgroup Analysis for CR Within 3 Months From KTE-X19 Infusion

Category	Subgroup	N	Achieved CR Within 3 Months from KTE-X19 Infusion		
			n	%	(95% CI)
Age	<65 Years	46	23	50%	(35, 65)
	>=65 Years	8	5	63%	(25, 92)
Sex	M	33	18	55%	(36, 72)
	F	21	10	48%	(26, 70)
Race	White	36	21	58%	(41, 75)
	Other	9	1	11%	(0.3, 48)
	Missing	4	3	75%	(19, 99)
	Asian	3	2	67%	(9, 99)
	American Indian Or Alaska Native	1	1	100%	-
	Black Or African American	1	0	0%	-
Ethnicity	Not Hispanic Or Latino	41	24	59%	(42, 74)
	Hispanic Or Latino	11	3	27%	(6, 61)
	Missing	2	1	50%	(1.3, 99)
Prior blinatumomab	N	29	19	66%	(46, 82)
	Y	25	9	36%	(18, 58)
Prior inotuzumab	N	42	23	55%	(39, 70)
	Y	12	5	42%	(15, 72)
Prior allogeneic HSCT	N	31	16	52%	(33, 70)
	Y	23	12	52%	(31, 73)
Disease status	Refractory relapse	25	11	44%	(24, 65)
	Primary refractory disease	14	9	64%	(35, 87)
	Second or later untreated relapse	11	6	55%	(23, 83)
	First untreated relapse	4	2	50%	(6.8, 93)

Source: FDA Analysis

Reviewer comment: *See Section 8.1.4 regarding the basis for regulatory approval for this sBLA which is CR withing the first 3 months from KTE-X19 infusion.*

Efficacy Results – Exploratory or COA (PRO) endpoints

Data:

Patient reported outcomes, as measured by the EQ-5D-5L VAS, remained stable or improved relative to values at baseline for the majority of subjects following treatment with KTE-X19 (≥ 70% of evaluable subjects considered stable or improved across time points from Day 28 through Month 12). Additional information is provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 12.1; ADSL, ADQS.

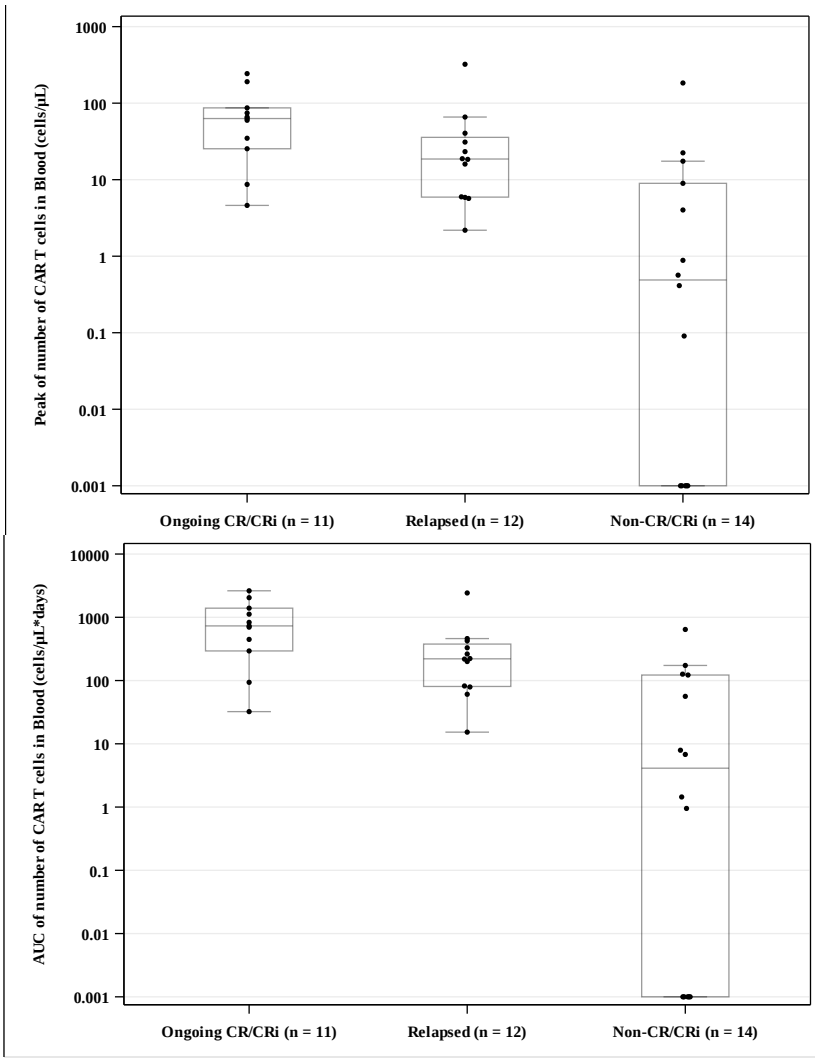
The FDA's Assessment:
Study ZUMA-3 was an open-label study. Patient-reported outcomes in open label studies may be impacted by subjects' knowledge of the treatment received. Moreover, no placebo group was present in the study to assess any potential advantage in patient-reported outcomes. Results of any exploratory analysis conducted by the Applicant should be interpreted with caution.

More importantly, although the Applicant proposed to include PRO measures as a secondary endpoint, the Applicant did not submit the PRO instruments for FDA's review by the clinical outcome assessment team. Notably, the Applicant does not intend to include PRO data in labeling. Therefore, PRO data, namely EQ-5D-5L VAS, were not reviewed in this submission.

Dose/Dose Response

Data:
Anti-CD19 CAR T-cell levels in blood (median peak and AUC_{0-28}) were examined for associations with ongoing response. In Phase 2, the median peak anti-CD19 CAR T cell levels and AUC_{0-28} were the highest in subjects with an ongoing CR/CRi, followed by subjects who relapsed, and were lowest in subjects who did not achieve a CR or CRi (Figure 7). Additional information is in m5.3.4.2, ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Section 2.3.1.1.2.

Figure 7 Kite - Anti-CD19 CAR T-cell Peak (Cells/µL) and AUC_{0-28} (Cells/µL•Days) in Blood by Ongoing Response Based on Central Assessment at Primary Analysis Data Cutoff (Phase 2, mITT Analysis Set)



Data cutoff date = 09SEP2020
Abbreviations: AUC, area-under-the-curve; CAR, chimeric antigen receptor, CR, complete remission; CRi, complete remission with incomplete hematologic recovery; mITT, modified intent-to-treat.
Peak is defined as the maximum number of CAR T cells in blood measured after infusion.
AUC_{0-28} is defined as the AUC in a plot of number of CAR T cells in blood against scheduled visit from Day 0 to Day 28.
Non-CR/CRi is defined as subjects who had neither CR nor CRi by the primary analysis data cutoff.
Fourteen subjects were censored at the time of allo-SCT (9 subjects) or at the start of new anticancer therapy (5 subjects).
Source: m5.3.4.2 ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Figure 5 and Figure 6; ADCART, ADEFF, ADSL.

The Applicant's Position:

An association was observed between anti-CD19 CAR T-cell peak expansion and AUC_{0-28} in blood and ongoing response.

The FDA's Assessment:

The Applicant indicated (Study KTE-C19-103 CSR Section 7.4.4.3) that the KTE-X19 starting dose chosen for the Study (2 x 10^6 cells/kg) was based on excess toxicity observed using 3 x 10^6 cells/kg of a predecessor product. Lower doses (0.5 and 1 x 10^6 cells/kg) were added to the protocol to determine if doses with potentially less toxicity would provide similar efficacy.

Across the phases of ZUMA-3, there were 99 subjects with r/r ALL treated with KTE-X19 using doses of 0.5 - 2 x 10^6 cells/kg. Table 19 shows the proportions of subjects who achieved CR within 3 months by the target dose of KTE-X19.

Table 19 FDA - ZUMA-3: CR Rate by KTE-X19 Target Dose

		Achieved CR Within 3 Months from Infusion		
Target KTE-X19 Dose	**N**	**n**	**%**	**(95%CI)**
0.5 x 10^6 cells/kg	16	6	38%	(15%, 65%)
1 x 10^6 cells/kg	77*	42	55%	(43%, 66%)
2 x 10^6 cells/kg	6	3	50%	(12%, 88%)

Source: FDA Analysis
*Excluding Subject ID (b) (6) who was excluded from FDA's efficacy evaluable population because the subject lacked presence of BM blasts at baseline disease assessment post-bridging chemotherapy.

It should be noted that there was a potential impact of formulation on efficacy that might affect interpretation of the dose-response analysis. Seven subjects in Phase 1 received KTE-X19 formulated in 40 mL rather than 68 mL (see Section 4.2); all seven were in the KTE-X19 0.5 x 10^6 cells/kg target dose group. A CR within 3 months of infusion was achieved by one (14%) of the seven subjects with a 40 mL product and by five (56%) of the nine subjects with a 68 mL product.

Additional Analyses Conducted on the Individual Trial

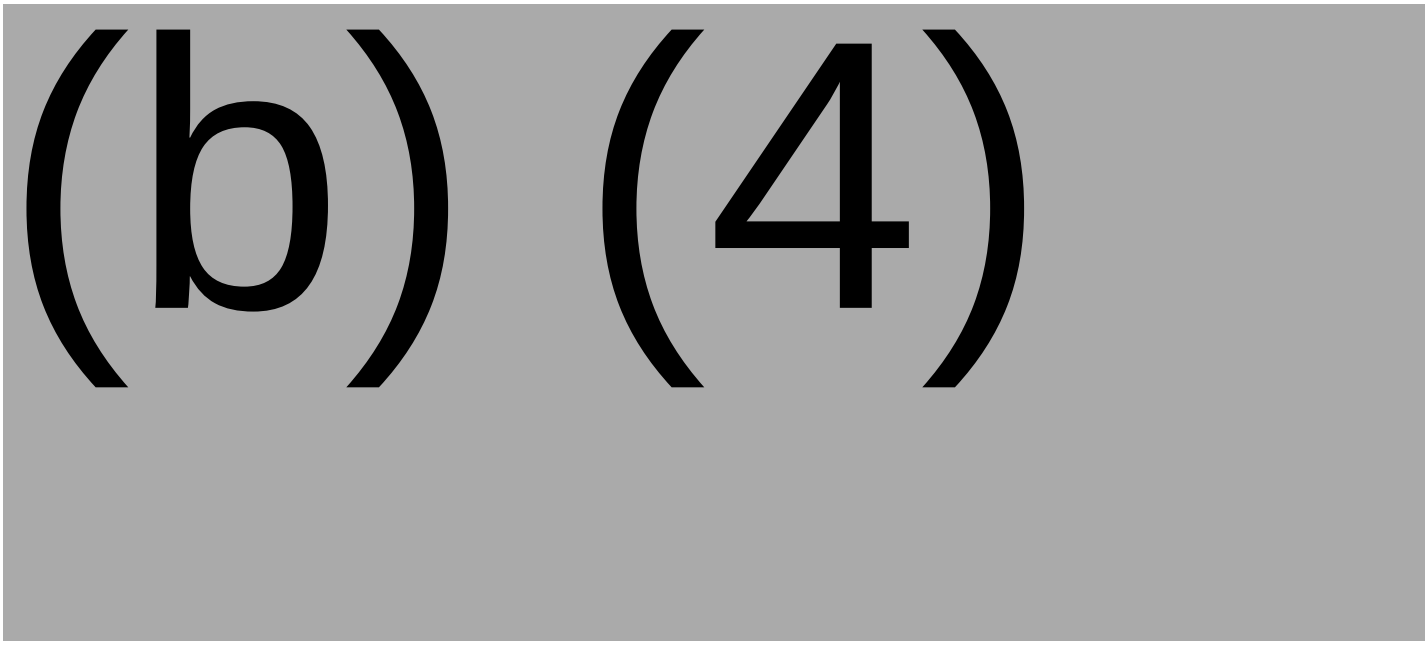
Data:

Two subjects in Phase 2 were retreated with KTE-X19; both subjects had (b) (4) to retreatment, and 1 of the subjects had died as of the data cutoff date. Additional information is provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 9.4.2; ADSL, ADBASE, ADEFF, ADTTE.

The FDA's Assessment:

Retreatment

Subjects were permitted to receive one additional KTE-X19 infusion provided the subject achieved remission of leukemia (CR, CRh, or CRi) at their Month 3 or later disease assessment following the initial KTE-X19 infusion and subsequently progressed. The assessment of efficacy was to be reported separately for subjects who were retreated.



8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Methods

The Applicant proposed the indication "for treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)".

Issues with the clinical development program: The clinical development program for this indication included only one trial, ZUMA-3, a single-arm Phase 1-2 trial. In general, multiple adequate and well-controlled trials or one adequate and well-controlled trial with confirmatory

evidence would be required to support a marketing application.[7] The Applicant proposed to use the Phase 2 portion of ZUMA-3 as the pivotal trial. At the Type B meeting on February 2, 2021, FDA requested that all data from the Phase 1 portion be submitted as confirmatory evidence.

Issues with the pivotal trial design: The Phase 2 portion of ZUMA-3 was a single-arm trial of KTE-X19 at the proposed dose for treatment of patients with relapsed or refractory Pre-B ALL. The study was powered to exclude an OCRR (CR+CRi) of 40% by independent review when the true response rate was 65% in all patients treated with KTE-X19 (mITT) in Phase 2. Three issues were identified with the study design.

- First, CR rather than OCR (the primary endpoint in ZUMA-3) is the accepted endpoint for regulatory decision-making when supported by duration of CR. CR per independent review is listed in ZUMA-3 as a secondary endpoint to be reported descriptively. Therefore, reliance on the CR results for regulatory decision-making would be conditional on the study first meeting the primary objective. This issue was discussed with the Applicant at the Type B meeting on 5/15/2018.

- Second, there was no timing prespecified for the response assessment to be used for the analysis of the primary endpoint. The SAP indicates "The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT analysis set has had the opportunity to complete the 6-month disease assessment after KTE-X19 infusion", which would allow the latest visit to be used for analysis of the primary endpoint without regard for the different lengths of follow-up for different subjects. In general, responses to induction chemotherapy are expected to occur within 42 days from the start of therapy for treatments of acute leukemia. Delay in count recovery has been observed after CAR T-cell treatments, but the risks from prolonged cytopenias could at least partially negate the clinical benefit. Prior precedent for CAR T-cell therapy for ALL was CR within 3 months from infusion.[8]

- Third, the protocol included a secondary endpoint of "MRD negative rate", defined as the incidence of MRD < 10^{-4}, and it prespecified testing in comparison to a 30% rate with a one-sided alpha of 0.025 (Protocol Section 10.8.3 and SAP Section 3.3). The definition of the endpoint did not include any criteria for timing or need for count recovery for the assessment of this endpoint. FDA has accepted MRD < 10^{-4} at the time of CR as supporting

[7] *"Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Guidance for Industry (December 2019)"* at https://www.fda.gov/media/133660/download
[8] US Prescribing Information for Kymriah, available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189

evidence of effectiveness for ALL.[9] The SAP also includes "Rate of MRD- CR" as a secondary endpoint planned for only descriptive statistics (SAP Section 9.5.3).

The review team concluded that as long as the study met the primary objective, these issues did not negate use of an analysis of CR that would inform regulatory decision-making.

Primary Endpoint

The Applicant reported that an OCR was achieved by 39 (70.9%; 95% CI 57, 82) of the 55 subjects treated with KTE-X19 in the Phase 2 portion of ZUMA-3. Since the lower bound of the 95% CI exceed the prespecified limit of 40%, they concluded that the primary objective was met. Excluding the one subject who did not have evidence of active disease at treatment baseline and using FDA-adjudicated responses, FDA identified an OCR in 35 (64.8%; 95% CI (50.6, 77.3) of 54 subjects and confirmed that the primary objective was met.

FDA considers a CR within 3 months from start of therapy to reflect a clinical benefit for patients with r/r Pre-B ALL treated with CAR T-cell therapies. Table 21 shows FDA's adjudicated CR rate at any time on study through the data cutoff date and through the Month 3 visit for the Phase 2 population and, side-by-side, for the 23 subjects in Phase 1 treated at the proposed KTE-X19 target dose of 1 x 10^6 cells/kg. The CR rate through the Month 3 visit was 51.9% with a lower bound of 37.8% in the Phase 2 cohort, and the results from Phase 1 are supportive. With a median follow-up for responders of 7.1 months, the median DOCR was not reached. The median time to CR was 56 days (range: 25 to 86 days). Because the Phase 1 study was hypothesis-generating and not an adequate and well-controlled trial, the review team recommends including only the outcomes from Phase 2 in labeling.

[9] *"Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment. Guidance for Industry. (January 2020)"* available at https://www.fda.gov/media/134605/download

Table 21 FDA - ZUMA-3: Analysis of CR and DOCR in Subjects Treated at the Target KTE-X19 Dose of 1 x 10^6 Cells/Kg

	Phase 2 mITT (N=54)[a]	Phase 1 (N=23)
At Any Time on Study		
CR rate, n (%) [95% CI]	29 (54%) (39.6, 67.4)	15 (65.2%) (42.7, 83.6)
Median duration of CR [95% CI] [b]	NE (9.6, NE)	10.1+ (0.3+, 22.7+)
Through Month 3 Visit		
CR rate, n (%) [95% CI]	28 (51.9) (37.8, 65.7)	14 (60.9%) (38.5, 80.2)
Median duration of CR [95% CI] [d]	NE (9.6, NE)	6.9+ (0.3+, 22.7+)

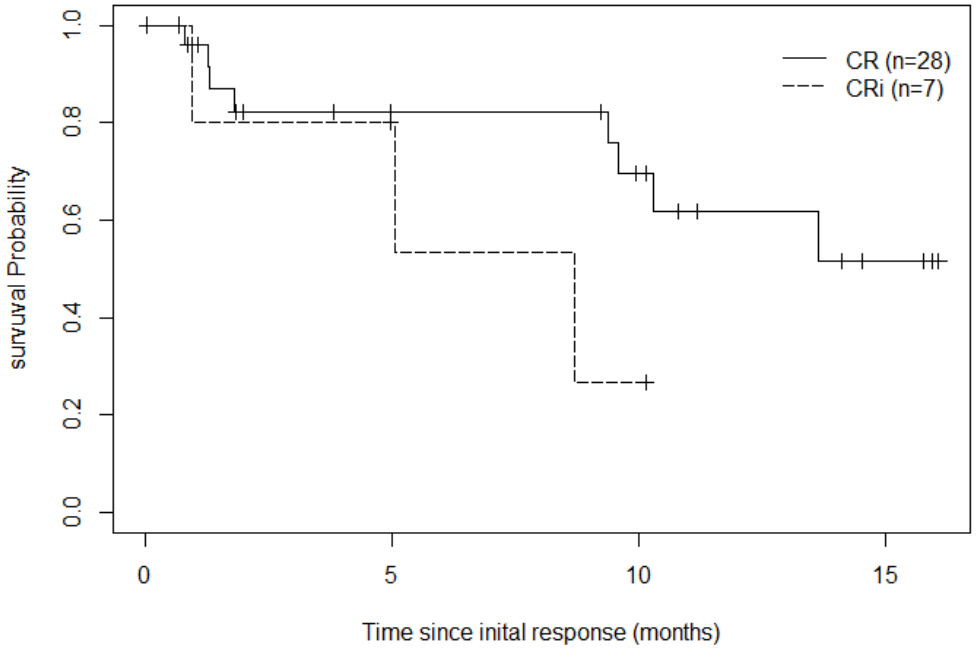
Source: FDA Analysis using FDA-adjudicated outcomes
[a] Includes only the 54 subjects with evidence of active disease at treatment baseline
[b] Kaplan-Meier estimate with a median follow-up of 5.0 months (0.03+, 16.1+)
[c] Due to the small number of subjects, the observed median and range are displayed
[d] Kaplan-Meier estimate with a median follow-up of 7.1 months (0.03+, 16.1+)

Durability of Response

With a median follow-up of 7.1 months, the duration of CR in the pivotal cohort was not estimable (Table 21 above and Figure 8 below). The Kaplan-Meier estimate of the proportion of subjects whose CR lasted at least 12 months is 55% (Table 13 in Section 8.1.2). It should be noted that the proportion of subjects with a 12-month DOCR is not considered an efficacy endpoint, but rather is used to provide context when the DOCR is not estimable.

The review team concluded that the CRs following treatment with KTE-X19 exhibit durability. The conclusion is supported by the median DOR of 6.9+ months for the subjects in the Phase 1 (See Table 19).

Figure 8 FDA - ZUMA-3: Duration of Response for Responders Within 3 Months of KTE-X19 Infusion



Source: Statistical Reviewer

Subpopulations

The demographic and baseline disease characteristics of the study population were described in Section 8.1.2 above. The study population was concluded to be representative of the intended population. Table 18 in Section 8.1.2 shows the subpopulation analysis for CR within 3 months from infusion of KTE-X19. With the caveat that some groups have numbers too small to allow a credible analysis, a treatment effect is noted across subpopulations. The review team concludes that the results support the proposed intended population of adult patients with relapsed or refractory Pre-B ALL.

Secondary and Other Endpoints

The protocol and SAP listed multiple secondary endpoints, of which only CR with MRD < 10^{-4} would be considered for a labeling claim on the basis of a single-arm trial. However, because the CDRH reviewer determined that the MRD assay used in ZUMA-3 was not analytically valid for the < 10^{-4} cutoff (see Section 4.3), the review team concluded that the MRD data from ZUMA-3 are not sufficient to support a labeling claim for KTE-X19.

Dose/Dose Response

The rationale for the selection of the initial dose for Phase 1 of ZUMA-3 was based on two (b) (4) studies that used a predecessor product with the same CAR construct as in ZUMA-3 – one study was conducted at the (b) (4) with r/r ALL (Study (b) (4)), and the other was conducted at the (b) (4) in adults with r/r B-cell malignancies (Study (b) (4)). No formal dose-ranging study was conducted prior to conduct of the pivotal Phase 2 trial.

In a pooled analysis, efficacy was assessed by dose using all subjects in the Phase 1 and Phase 2 portions of ZUMA-3. As shown in Table 19, the CR rate for the KTE-X19 0.5 x 10^6 cells/kg cohort (38%) was numerically less than with higher doses, and the CR rate with 2 x 10^6 cells/kg (50%) did not appear to be greater than with 1 x 10^6 cells/kg (55%). Of note, the CR rate was less in the 0.5 x 10^6 cells/kg cohort only for those who received the 40 mL volume product (14%); otherwise, the CR rate using the 68 mL product was similar across doses (50-56%). Consequently, although there is no evidence to suggest that the 1 x 10^6 cells/kg dose is not appropriate, given the small number of subjects treated with other doses, it is not clear that 1 x 10^6 cells/kg is optimal.

Additional Efficacy Considerations

Extrapolation to the Pediatric Population

The Clinical Pharmacology Reviewer reported that the Applicant did not provide sufficient data from ZUMA-4 to assess PK, ER, or exposure matching for pediatric subjects. The review team concludes that there is not sufficient information to allow extrapolation of efficacy to pediatric patients.

Efficacy at Retreatment

(b) (4)

8.1.4. Integrated Assessment of Effectiveness/Assessment of Efficacy Across Trials

The Applicant's Position:
This sBLA is based on efficacy results from ZUMA-3 only; thus, this section is not applicable.

The FDA's Assessment:
The results of FDA's analysis of ZUMA-3 showed a 51.9% rate of CR within 3 months of infusion of KTE-X19 with a lower bound of 37.8% in the pivotal Phase 2 cohort, a duration of CR that is estimated to exceed 12 months for more than half the subjects, and similar outcomes in the subgroup of subjects in the Phase 1 study treated with the recommended dose of KTE-X19. A treatment effect was observed across the subpopulation analyses. This is concluded to be substantial evidence of the effectiveness of KTE-X19 for treatment of adult patients with relapsed or refractory Pre-B ALL.

8.2. Review of Safety

Data:
Safety was assessed among all 55 subjects treated with any dose of KTE-X19 in ZUMA-3 Phase 2. Additional safety data are provided from 4 studies of KTE-X19 in subjects with r/r MCL (KTE C19-102 [ZUMA-2] and KT-US-472-0118 [ZUMA-18] Cohort 1 pooled, n = 103 subjects treated); pediatric r/r ALL (KTE-C19-104 [ZUMA-4] n = 36 subjects treated); and r/r chronic lymphocytic leukemia (CLL) (KTE-C19-108 [ZUMA 8], n = 9 subjects treated). All 4 studies are summarized in Table 5 and in m2.7.4, ZUMA-3 Summary of Clinical Safety.

Cytokine release syndrome (CRS) and neurologic adverse events (AEs) associated with KTE-X19 treatment mostly occurred in the first month after cell infusion and were largely reversible and manageable with medical intervention. The overall rates of CRS and neurologic AEs in ZUMA-3 were generally comparable to those observed in ZUMA-2, although a higher incidence of Grade 3 or higher CRS was observed in ZUMA-3.

The Applicant's Position:
Risks associated with KTE-X19 have been well characterized and no new safety signals were identified relative to those observed in adult patients with r/r MCL in ZUMA-2 {Wang 2020}.

8.2.1. Safety Review Approach

The Applicant's Position:
Safety assessments included the incidence of AEs, clinically significant changes in laboratory values, antibodies to KTE-X19, and the occurrence of replication-competent retrovirus (RCR) in subjects' blood. Investigators were to report all AEs that occurred from enrollment (ie, leukapheresis) through 3 months after KTE-X19 infusion. After Month 3 and until 24 months, or disease progression, whichever occurred first, only the

following targeted AEs and serious adverse events (SAEs) were to be collected: neurologic events, hematologic events, infections, graft-versus-host disease (GVHD), autoimmune disorders, and secondary malignancies. All SAEs considered related to KTE-X19 were to be reported regardless of when they occurred. All deaths that occurred from signing of the ICF through the end of the study were to be reported. Use of concomitant medications for treatment of CRS and neurologic events was also reported.

The FDA's Assessment:

Selection of the Safety Population for Review

There were 248 subjects from 5 clinical trials in the ISS database. Table 22 shows the numbers of subjects exposed by trial and KTE-X19 target dose.

Table 22 FDA - Number of Subjects Exposed to KTE-X19 by Trial and Target Dose

Study	Population	Number of Subjects at Target KTE-X19 Cell Dose x 10^6/kg		
		0.5	**1.0**	**2**
KTE-C19-102; ZUMA-2	Adults with R/R MCL	14	0	68
KTE-C19-103; ZUMA-3	Adults with R/R ALL	16	78	6
KTE-C19-104; ZUMA-4	Children with R/R ALL/NHL	0	32	4
KTE-C19-108; ZUMA-8	Adults with R/R CLL/SLL	0	6	3
KT-US-472-0118; ZUMA-18	Expanded Access R/R MCL	0	0	21
All trials		30	116	102

Source: FDA Analysis

The ZUMA-3 Study was the basis for the primary safety review. Data from ZUMA-2, ZUMA-4, ZUMA-8 and ZUMA-18 were considered supportive. FDA's safety review focused on three analysis sets:

- The 248 subjects in the ISS were considered in the overview of fatal adverse reactions and in an analysis of the CRS and neurotoxicity across diagnoses to inform labeling.
- The 100 subjects treated with any cell dose in ZUMA-3 were used for the assessment of dose-toxicity relationships.
- The 78 subjects treated at the target KTE-X19 dose level of 1 x 10^6 cells/kg in ZUMA-3 were the main population for detailed development of the safety profile for the recommended dose in the intended population.

The clinical safety review was primarily based on analysis of data submitted for the safety analysis set which comprised 78 subjects enrolled and treated with KTE-X19 dose of 1 x 10^6 anti CD19 CAR T cells/kg in the ZUMA-3 Phase 1 and Phase 2 Study. Because the treatment regimen was similar between the Phase 1 and Phase 2 cohorts who received KTE-X19 dose of 1 x 10^6 anti-CD19 CAR T cells/kg, safety analyses of ZUMA-3 study were performed for each cohort side by side and were also pooled for both cohorts at that cell dose. The data from pooled 1 x 10^6 anti-CD19 CAR T cells/kg cohorts will be presented in the label.

The database lock for the 120-day safety update report (SUR) was 19 March 2021. The primary safety review was based on the data in the initial submission of the sBLA with the data cutoff date of 09 September 2020. Key findings in the SUR are provided at the end of Section 8.2.4.

Caveats for Pooling

During the course of conduct of ZUMA-3, the protocol was amended to update the management strategy for CRS and neurotoxicity. In the original protocol (07 May 2015), tocilizumab 4-8 mg/kg was to be considered for treatment of subjects with comorbidities who developed Grade 2 CRS, for subjects with Grades 3-4 CRS, or for subjects with CRS and LVEF of 40%, creatinine more than 3 times baseline, or who failed vasopressor therapy for 36 hours; methylprednisolone (MP) 1 mg/kg q 12 hours was to be used if tocilizumab was ineffective for CRS; and steroids were to be considered for subjects with severe or life-threatening neurotoxicity. The major revisions to the toxicity management strategy in the amendments included:

- For use of tocilizumab for treatment of CRS: the recommendation was changed to 8 mg/kg q 4-6 hours for 3 doses for subjects in Amendment 3, for all subjects with grades 2-4 CRS in the 22 May 2017, version of the IB, and for up to 4 doses during use of Amendment 5.

- For use of steroids for treatment of CRS: the recommendation was changed to consider MP 1 mg/kg BID for Grades 2-3 CRS and to give 1 gm/day for Grade 4 CRS in Amendment 3; to consider MPE 1 mg/kg BID for tocilizumab failure for Grade 2 CRS, to give MP 1 mg/kg BID for all Grade 3 CRS, and to give 1 gm/day for Grade 4 CRS in the 22 May 2017, version of the IB.

- For use of tocilizumab for prevention of CRS: a dose of 8 mg/kg 36 hours after infusion of KTE-X19 was required only in Amendment 4.

- For use of tocilizumab for treatment of neurotoxicity: a dose of 4-8 mg/kg was recommended for Gr 3-4 in Amendment 1, and the recommendation for use of tocilizumab for neurotoxicity without CRS was removed starting with the 22 May 2017, version of the IB.

- For use of steroids for treatment of neurotoxicity: dexamethasone 10 mg QID was recommended in Amendment 1 for Grade 3-4 that failed tocilizumab; dexamethasone or MP 1 mg/kg for Grade 3 that failed tocilizumab and MP 1 gm/day for all Grade 4 was recommended in Amendment 3; and dexamethasone 10 mg QID for all Grade 2-3 and MP 1 gm/day for Grade 4 was to be used starting with the 22 May 2017, version of the IB. Use of high-dose steroids for treatment of cerebral edema was added to the 08 June 2017, version of the IB.

The recommended management of CRS and neurotoxicity proposed for labeling is essentially that in the June 8, 2017, version of the IB and protocol Amendment 5. The Applicant indicated that immediate use of this management plan was conveyed in a Dear Investigator Letter on 12 June 2017, and that the management should be considered applicable to all subjects treated after that date (Applicant's Response to Information Request received 07 May 2021). The impact of the change in management over time is assessed in this safety review, but the majority of the analyses in the safety analysis set include a pool of all subjects without regard to the version of the safety management instructions in use at the time of treatment.

The safety analysis set included all subjects who received KTE-X19 at a target dose of 1 x 10^6 anti-CD19 CAR T cells/kg, rather than the actual dose received. This was considered acceptable given that the majority of subjects (97%) received a dose within 10% of the planned KTE-X19 dose.

Anticipated Safety Issues

Overall, the safety profile of KTE-X19 was anticipated to be consistent with what was observed in the original BLA submission. The main known adverse reactions of interest that would require characterization in the new intended population include CRS and neurotoxicity. As indicated in Section 4.2, hypersensitivity reactions are a potential risk.

8.2.2. Review of the Safety Database

Overall Exposure

Data:
In ZUMA-3 Phase 2, the median weight-adjusted dose of KTE-X19 was 1.0 x 10^6

anti-CD19 CAR T cells/kg. In the combined studies ZUMA-2 and ZUMA-18 (adult MCL), the median weight-adjusted dose of KTE-X19 was 2.0 $x10^6$ anti-CD19 CAR T cell/kg; in ZUMA-4 (adolescent/ pediatric ALL), the median weight-adjusted dose of KTE-X19 was 1.0 $x10^6$ anti-CD19 CAR T cell/kg, and in ZUMA-8 (adult CLL), the median weight-adjusted dose of KTE-X19 was 1.0 $x10^6$ anti-CD19 CAR T cell/kg (m2.7.4, ZUMA-3 Summary of Clinical Safety, Table 8 and Table 9; ADSL, ADDA, ADEX).

The FDA's Assessment:
In the efficacy population, 53 subjects (98%) received within 10% of the planned total dose of KTE-X19. Two subjects (ID (b) (6)) received actual dose of 0.9 x 10^6 anti-CD19 CAR T cells/kg. All subjects who weighted ≥ 100 Kg received a flat dose of 1 x 10^8 anti-CD19 CAR T cells except for the one subject (ID (b) (6))who weighed > 100 kg and received a flat dose of 0.81 x 10^8 anti-CD19 CAR T cells, rather than the planned flat dose of 1 x 10^8 anti-CD19 CAR T cells due to OOS product. Among 78 subjects in the safety analysis set, 97% received KTE-X19 at dose of 0.9 to 1 x 10^6 anti-CD19 CAR T cells/kg.

Treatment exposure in ZUMA-3 Phase 1 and Phase 2 is summarized in Table 23. Overall, the median time from enrollment to start of conditioning chemotherapy (CC) (i.e., lymphodepletion (LD)) was 24 days (range: 13 to 87 days), and the median time from enrollment to KTE-X19 infusion was 29 days (range: 18 to 91 days).

Table 23 FDA - ZUMA-3: Summary of Treatment Exposure

Exposure	Phase1 N = 23 n (%)	Phase2 N = 55 n (%)	Overall N = 78 n (%)
Days from CC to KTE Infusion			
Mean (SD)	5.4 (3.7)	6.3 (4.2)	6.1 (4)
Median (Range)	4 (4–18)	4 (4–25)	4 (4–25)
Days from Enrollment to CC			
Mean (SD)	24.2 (12.2)	29.3 (16.2)	27.8 (15.2)
Median (Range)	21 (14–72)	24 (13–87)	24 (13–87)
Days from Enrollment to KTE Infusion			
Mean (SD)	29.7 (12.5)	35.6 (15.9)	33.8 (15.2)
Median (Range)	26 (18–76)	30 (20–91)	29 (18–91)
Days from KTE Infusion to Hosp Discharge			

Exposure	Phase1 N = 23 n (%)	Phase2 N = 55 n (%)	Overall N = 78 n (%)
Mean (SD)	21.6 (15.5)	21.6 (14.7)	21.6 (14.9)
Median (Range)	16 (7–72)	17 (7–77)	17 (7–77)
Days from Leukapheresis to CC			
Mean (SD)	22.2 (6.3)	25.1 (8.6)	24.3 (8)
Median (Range)	21 (14–37)	24 (13–56)	22.5 (13–56)
Days from Leukapheresis to KTE Infusion			
Mean (SD)	27.6 (7.4)	31.5 (8.6)	30.3 (8.4)
Median (Range)	26 (18–41)	29 (20–60)	29 (18–60)
Total BSA adjusted dose Cyclophosphamide Period 01 (mg/m2)			
Mean (SD)	900 (0)	900 (0)	900 (0)
Median (Range)	900 (900–900)	900 (900–900)	900 (900–900)
Total BSA adjusted dose Fludarabine Period 01 (mg/m2)			
Mean (SD)	75 (0)	74.9 (0.5)	74.9 (0.5)
Median (Range)	75 (75–75)	75 (71–75)	75 (71–75)
Total Dose Received (10^6 CAR + T cell/kg)			
Mean (SD)	1 (0.1)	1 (0.1)	1 (0.1)
Median (Range)	1 (0.5–1)	1 (0.5–1)	1 (0.5–1)
Total Number of CAR + T cells (10^6)			
Mean (SD)	74.7 (17.8)	77.4 (16.8)	76.6 (17)
Median (Range)	76.7 (46.5–101)	75.7 (39.3–101)	75.8 (39.3–101)
Total Number of T cells Infused (10^6)			
Mean (SD)	147.1 (56.2)	138.9 (43.9)	141.3 (47.7)
Median (Range)	125.9 (82.4–314.2)	128.4 (65.5–277.8)	127.5 (65.5–314.2)
Transduction Ratio			
Mean (SD)	0.5 (0.2)	0.6 (0.1)	0.6 (0.1)
Median (Range)	0.5 (0.2–0.8)	0.6 (0.3–0.8)	0.6 (0.2–0.8)

Source: FDA Analysis. ADSLFDA, ADEX
Abbreviation: CC: conditioning chemotherapy

Reviewer comment: *Most subjects received the product at 1 x 10^6 anti-CD19 CAR T cells/kg or, for subjects weighing more than 100 kg, 1 x 10^8 anti-CD19 CAR T cells. Too few subjects received the product at alternative doses to adequately support expanding the target dose to a defined dose range.*

Overall, exposure to KTE-X19 was within the target planned in the study protocol and is adequate to support characterization of the safety profile of KTE-X19.

Relevant Characteristics of the Safety Population

Data:
Study populations included in the safety analysis of KTE-X9 are summarized in Table 5. Demographic data for the 55 subjects who received KTE-X19 in ZUMA-3 Phase 2 are summarized in Table 8. In the combined studies ZUMA-2 and ZUMA-18, the median age was 65.0 years, 53 subjects (51%) were ≥ 65 years of age, 84 subjects (82%) were male, and 92 subjects (89%) were White. The median age of subjects in ZUMA-4 was 11.0 years, 33 subjects (92%) were < 18 years of age, 23 subjects were male (64%), and 24 subjects (67%) were White. The median age of subjects in ZUMA-8 was 61.0 years, 2 subjects (22%) were ≥ 65 years of age, 5 subjects (56%) were male, and 8 subjects (89%) were White (m2.7.4, ZUMA-3 Summary of Clinical Safety, Section 1.4, Table 12; ADSL).

The FDA's Assessment:
As stated earlier, FDA's safety analysis set included all 78 subjects from ZUMA-3 Phase 1 (N=23) and Phase 2 (N=55) Study who received KTE-X19 at target dose of 1 x 10^6 anti-CD19 CAR T cell/kg (maximum of 1 x 10^8 anti-CD19 CAR T cells). Demographics characteristics for subjects in the safety analysis set are presented in Table 24. The median age was 42.5 years (Range: 18-84 years old). More females were treated in the Phase 1 study compared to the Phase 2. Whites and non-Hispanic were the predominant race and ethnic groups, and the majority of subjects were treated in the US.

Table 24 FDA - ZUMA-3: Demographic Characteristics in the Safety Analysis Set

Demographic Group	Phase1 N = 23 n (%)	Phase2 N = 55 n (%)	Overall N = 78 n (%)
Age			
<65	19 (83)	47 (85)	66 (85)
>=65	4 (17)	8 (15)	12 (15)
<75	22 (96)	54 (98)	76 (97)

Demographic Group	Phase1 N = 23 n (%)	Phase2 N = 55 n (%)	Overall N = 78 n (%)
>=75	1 (4.3)	1 (1.8)	2 (2.6)
Mean (SD)	45.6 (17.6)	42.1 (16.1)	43.2 (16.5)
Median (Range)	45 (18–77)	40 (19–84)	42.5 (18–84)
Sex			
F	14 (61)	22 (40)	36 (46)
M	9 (39)	33 (60)	42 (54)
Race			
White	19 (83)	37 (67)	56 (72)
Asian	2 (9)	3 (5)	5 (6)
Other	1 (4.3)	9 (16)	10 (13)
Native Hawaiian or Other Pacific Islander	1 (4.3)	0	1 (1.3)
Missing	0	4 (7)	4 (5)
American Indian or Alaska Native	0	1 (1.8)	1 (1.3)
Black African or African American	0	1 (1.8)	1 (1.3)
Ethnicity			
Not Hispanic of Latino	12 (52)	42 (76)	54 (69)
Hispanic or Latino	11 (48)	11 (20)	22 (28)
Missing	0	2 (3.6)	2 (2.6)
Country			
USA	23 (100)	41 (75)	64 (82)
France	0	10 (18)	10 (13)
Germany	0	3 (5)	3 (3.8)
Netherland	0	1 (1.8)	1 (1.3)

Source: FDA Analysis. ADSLFDA

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
Baseline characteristics for the subjects in ZUMA-3 Phase 2 are summarized in Section Other Baseline Characteristics. In the combined studies ZUMA-2 and ZUMA-18, 34% of subjects were refractory to last therapy, 32% had relapsed after last therapy, and 34% had relapsed after auto-SCT; 40% had had ≥ 4 lines of previous therapy. In ZUMA-4, 25% of subjects had primary refractory disease, 28% had relapsed or had refractory disease after allo-SCT, and 47% were relapsed or refractory to second or greater line therapy; 8% had had ≥ 4 lines of previous therapy. In ZUMA-8, all subjects had had ≥ 4 lines of previous therapy (m2.7.4, ZUMA-3 Summary of Clinical Safety, Section 1.4.2, Table 13; ADSL, ADBASE).

The FDA's Assessment:
Among 78 subjects in the safety analysis set, 56 (72%) subjects had ECOG performance status of 1, while 22 (28%) subjects had ECOG performance status of 0. Seventeen (22%) subjects had Ph+ ALL, 38 (49%) subjects had prior blinatumomab therapy, 17 (22%) had prior inotuzumab therapy, and 29 (37%) received prior allo HSCT. Other disease characteristics included primary refractory disease in 24 (31%) subjects, r/r to 2nd or greater line therapy in 60 (77%) subjects, and r/r after allo HSCT in 30 (38%) subjects.

Adequacy of the Safety Database

The Applicant's Position:

The size of the safety database for ZUMA-3, supported by supplemental data from the 4 studies in subjects with r/r MCL, pediatric r/r ALL, and r/r CLL (a total of n = 148 subjected treated with KTE-X19, Table 5), is considered adequate to support the benefit-risk assessment for the use of KTE-X19 in patients with r/r B-ALL and adequately represents the target patient population.

KTE-X19 was approved in the US on 24 July 2020 and in the EU on 14 December 2020 for the treatment of adult patients with r/r MCL. At the time of the writing of this document, no postmarketing data were available (m2.7.4, ZUMA-3 Summary of Clinical Safety, Section 6).

The FDA's Assessment:
The Reviewer agrees that the safety database is considered adequate to identify most common AEs, support the benefit-risk assessment, and represent the target patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
No issues relating to safety data integrity or quality were identified for ZUMA-3.

The FDA's Assessment:

After FDA's adjudication of safety data, FDA requested that the Applicant submit new datasets that reflect FDA's adjudication. The Applicant submitted the updated datasets (ADSLFDA, ADBASEFDA, ADAEFDA, ADCRSFDA, ADNEFDA, and ADSAFFDA) on 30 July 2021 under SN 0123. ADAEFDA included FDA grouped terms (GT). The datasets include a flag variable "FDAADJFL" which was added to reflect all changed records due to FDA adjudication. ADAEFDA was used for the analyses of safety in ZUMA-3, and ADAE in the ISS was used for analyses across trials.

Categorization of Adverse Event

The Applicant's Position:

> Treatment-emergent adverse events (TEAEs), hereafter referred to as AEs, were defined as AEs with an onset on or after the KTE-X19 infusion (AEs that occurred after retreatment were summarized separately). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0, and the severity of AEs was graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (ZUMA-3, ZUMA-2, and ZUMA-4) or version 5.0 (ZUMA-8 and ZUMA-18).
>
> AEs of special interest included important identified risks (CRS, neurologic AEs, cytopenias, infections, and hypogammaglobulinemia) and important potential risks (secondary malignancies, immunogenicity, RCR, tumor lysis syndrome, and aggravation of GVHD). Autoimmune disorders were also examined.
>
> CRS is induced by activated T cells upon engagement with the CD19 target. CRS was graded as a syndrome according to a modification of the criteria established by Lee and colleagues {Lee 2014} that did not include neurologic AEs as part of CRS. Individual symptoms associated with CRS were graded per CTCAE.
>
> Neurologic events were identified separately from CRS based on known neurologic toxicities associated with anti-CD19 immunotherapy {Topp 2015} and focused on central nervous system toxicity without regard to relatedness, temporal relationship, or concomitant conditions. Further, neurologic events were also identified via a second search strategy that was based on the MedDRA System Organ Classes (SOCs) of

psychiatric disorders and nervous system disorders; excluding 2 high-level group terms that are not likely to be neurologic AEs associated with CAR T-cell therapy; and adding 7 preferred terms (tinnitus, papilloedema, diplopia, vision blurred, paraesthesia oral, gait disturbance, and nerve injury). These events were then evaluated for potential inclusion as neurologic AEs. Additional information is in the m5.3.5.2, ZUMA-3 CSR Addendum.

Details of search strategies for AEs of special interest are described in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 7.7.10.6.3.

The FDA's Assessment:

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. AE severity was graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. CRS was reported and graded as a syndrome using a modification of the grading system proposed by Lee and colleagues (Lee et al, 2014)[10]. It should be noted that in the original Lee grading scale, neurologic AEs were included as symptoms of CRS. In the Applicant's modification of the Lee grading scale, neurologic AEs were not reported as part of the CRS syndrome; rather, they were reported separately and graded per NCI CTCAE v4.03. Individual symptoms comprising CRS were reported as separate AEs and graded per NCI CTCAE v4.03. For each syndrome reported, investigators were to indicate which specific symptoms (as noted by the AE reporting) were associated with that syndrome. The Applicant's method for CRS grading was consistent with that of ZUMA-2 study in subjects with r/r MCL the original BLA.

Grading of neurologic toxicity was per CTCAE criteria. The Applicant included two analyses methods to define neurologic toxicity (NT):

- Method 1 as defined by Topp et al 2015 [11]
- Method 2 as defined by FDA which uses the MedDRA system organ class (SOC) of psychiatric disorders and nervous system disorders excluding the following isolated (if not occurred with other NEs) high-level group terms (HLGT): sleep disorders and disturbances, and peripheral neuropathies. Other preferred terms (e.g., tinnitus, papilloedema, diplopia, vision blurred, paraesthesia oral, gait disturbance, nerve injury, and insomnia) were evaluated for potential inclusion as neurologic AEs if they occurred with other NEs.

[10] Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124 (2):188-95.

[11] Topp MS, Gokbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16 (1):57-66

Investigators were to report all AEs that occurred from enrollment (i.e., leukapheresis) through 3 months after KTE-X19 infusion. After Month 3 and until 24 months, or disease progression, whichever occurred first, only the following targeted AEs and SAEs were to be collected: neurologic events, hematologic events, infections, autoimmune disorders, and secondary malignancies. Subjects who were enrolled but not dosed with KTE-X19 were to be followed for AEs through 30 days after the last study-specific procedure or until initiation of a new anticancer therapy, whichever occurred first.

An SAE was defined as an AE that met at least one of the following serious criteria: fatal, life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, congenital anomaly/birth defect, or any other medically important serious event. SAEs were collected from screening.

The Applicant's definition of treatment-emergent adverse events (TEAEs) per protocol included any AE with an onset or worsening on or after KTE-X19 infusion in the safety population. A separated analysis of AEs that occurred from Leukapheresis until the start of conditioning chemotherapy, and from the start of conditioning regimen until the day before KTE-X19 infusion, were conducted and presented separately. TEAEs that occurred after retreatment with second dose of KTE-X19 were summarized separately and were not included in the primary analysis for safety.

Several AEs are presented, throughout the review memo, as grouped terms as defined by FDA's definition. The complete list of FDA grouped terms for all TEAEs is presented in Section 16.5. Unless otherwise specified all analyses and tables in FDA's assessment sections were generated by the FDA review team.

AEs and deaths were also assessed for the period from enrollment (i.e., leukapheresis) to the planned time of infusion to assess risks for subjects who did not receive KTE-X19 due to manufacturing issues or adverse events.

Reviewer comment: *Because CAR T-cell therapy is preceded by conditioning chemotherapy and because of the single arm study design, it is often difficult to parse out the causality of AEs. Therefore, adverse drug reactions (ADRs) were defined by the Reviewer as any TEAE occurring after the start of KTE-X19 infusion regardless of perceived relationship and causality with the investigational product.*

The Applicant reported AEs by preferred terms, which may underestimate the incidence of some AEs. To minimize underestimation of AE, 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.

The Applicant's definition of TEAEs is acceptable. Note that the terms AEs and TEAEs are used interchangeably in this review except when discussing adverse events that occurred during the leukapheresis or chemotherapy conditioning periods where the AEs were considered not treatment emergent.

In general, all grade AEs were counted by maximum toxicity (max tox) grade (i.e., multiple incidences of the same AE in one subject are counted once at the worst grade for this subject). For example, for Grade 3 AEs, the number of subjects who experienced any event with max tox Grade of 3 counted. This is different from the number of subjects who had a Grade 3 event, which is typically larger, as some will also have Grade 4 or 5 events.

Although the reviewer agrees to exclude isolated AEs of sleep disorders and disturbances from NT definition, AEs such as insomnia when occurring in setting of other NTs should be included in Method 2 "FDA's" definition. Also, for Method 2, in addition to SOCs of psychiatric and nervous system disorders, the Reviewer also searched for other AEs under other SOCs (e.g., general disorders, eye/ear disorders, respiratory disorders etc..) that were not classified as NTs and that overlapped with other NTs and therefore should be included in Method 2 definition of NT. Notably, isolated events (not overlapping with other neurologic or psychiatric symptoms) or AEs that started relatively late post-investigational product infusion, were not included in Method 2 definition.

Routine Clinical Tests

The Applicant's Position:

Routine clinical safety assessments included clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations. Specialty tests were conducted for RCR and antibodies to KTE-X19. Additional information is provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 7.5. The Schedules of Assessments are provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 7.5.1.

The FDA's Assessment:

See schedule of assessments in Table 49 and Table 50. Overall, the schedule of testing in ZUMA-3 is considered adequate for the assessment of safety.

8.2.4. Safety Results

Deaths

Data:

Deaths that occurred in ZUMA-3 Phase 2 are summarized in Table 25. Among the 55 treated subjects, 20 subjects (36%) had died as of the data cutoff date. Additional information is provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.6.

Table 25 Kite - Deaths in ZUMA-3 (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
Subjects who died, n (%)	20 (36)
Deaths that occurred ≤ 30 days after KTE-X19 infusion, n (%)	4 (7)
Deaths that occurred > 30 days through 3 months (92 days) after KTE-X19 infusion, n (%)	5 (9)
Deaths that occurred > 3 months (92 days) after KTE-X19 infusion, n (%)	11 (20)
Primary cause of death, n (%)	
Adverse event[a]	6 (11)
Progressive disease[a]	13 (24)
Other	1 (2)

Data cutoff date = 09Sep2020.

a Subjects with Grade 5 acute lymphocytic leukemia are categorized as "progressive disease" and excluded from the "adverse event" category in this table.

Source: m5.3.5.2, ZUMA-3 Primary Analysis CSR, Table 52; ADSL.

In the combined studies ZUMA-2 and ZUMA-18, 33 subjects (32%) had died as of the data cutoff date; out of these, 22 subjects (21%) died due to progressive disease (PD), and 7 (7%) due to AEs. In ZUMA-4, 16 subjects (44%) had died; out of these, 13 subjects (36%) died due to PD, and 2 (6%) due to AEs. In ZUMA-8, 3 subjects (33%) had died, all due to PD. Additional information is provided in m2.7.4, ZUMA-3 Summary of Clinical Safety, Section 2.2.3; ADSL.

The FDA's Assessment:

The table below summarizes the fatal adverse events and deaths due to the underlying malignancy within the first 3 months from KTE-X19 infusion across protocols as reported by the Applicant in the ISS. There were no fatal events as adjudicated by the Applicant that were unexpected terms.

Table 26 FDA - Summary of Applicant-Adjudicated Cause of Deaths within 3 Months from KTE-X19 Infusion in the ISS Dataset

			Fatal Adverse Events		Death from Primary malignancy	
Study	**Population**	**N**	**n**	**%**	**n**	**%**
KTE-C19-102	Adults with R/R MCL	82	2	2%	3	4%
KTE-C19-103	Adults with R/R ALL	100	10	10%	9	9%
KTE-C19-104	Children with R/R ALL/NHL	36	1	3%	2	6%
KTE-C19-108	Adults with R/R CLL/SLL	9	0	0%	1	11%
KT-US-472-0118	Expanded Access R/R MCL	21	2	10%	0	0%
All		248	15	6%	15	6%

Source: FDA Analysis

Among the 78 subjects in the safety analysis set, the median potential follow-up time was 19.2 months (range: 10.3, 47.9) and the median actual follow-up time was 13.1 months (range: 0.3, 47.5). Thirty-two (32) subjects (41%) died as of the data cutoff date; out of these, 27 (35%) subjects died of PD (5 of whom died of AEs in setting of PD), and five (6%) subjects died of AEs. Table 27 and Table 28 summarize the death events and FDA's adjudication of the root cause of death.

Twelve subjects died in the Phase 1 (two due to AEs) and 20 subjects in the Phase 2. CRS was ongoing at time of death in three subjects, one of whom died of cerebral edema and subsequent brain herniation.

Table 27 FDA - ZUMA-3: Summary of FDA-Adjudicated Deaths in the Safety Analysis Set

FDA Adjudicated Root Cause of Death	**Safety Analysis Set N=78 (%)**	**Safety Analysis Set N=78 (%)**
	Deaths	**Deaths within 30 days of KTE-X19**
All Deaths, n (%)	32 (41%)	4 (5%)
PD	27 (35%)	1 (1%)
AE in setting of PD	5 (6%)	1 (1%)
AR	4 (5%)	3 (4%)
Unrelated AE	1 (1%)	0

Source: FDA Analysis. ADSLFDA, ADAEFDA, Narratives, Case Report Forms
Abbreviations: AE: Adverse event; AR: Adverse reaction; PD: Progressive disease

Table 28 FDA - ZUMA-3: FDA Adjudication of Cause of Death

Subject ID	Day of Death	Applicant Cause of Death	FDA Adjudicated Root Cause of Death	FDA Comments
(b) (6)	231	Other: Hemorrhagic shock	DIC in setting of PD	On Day 231, the subject died due to hemorrhagic shock due to gastrointestinal bleed, disseminated intravascular coagulation (DIC), and PD.
(b) (6)	50	AE	Sepsis	The subject had sepsis that started on Day 27.
(b) (6)	309	AE	Viral infection (HSV viremia) post Allo SCT	The subject underwent allo SCT on Day 174. The subject had GVHD Day 209 to Day 246. HSV Viremia started on Day 298
(b) (6)	21	PD	CRS was ongoing in one subject with PD	The subject had hypoxia and dyspnea Day 6 to Day 21. The subject had Grade 2 CRS (fever, hypotension and hypoxia) (Day 1 to Day 5) and Gr 3 CRS (Day 6 to Day 21). Acute respiratory failure on Day 1 to Day 7. Day 8 the subject had 92% Circulating lymphoblasts. IL-6 peaked from baseline by 3-fold on Day 7.
(b) (6)	8	AE	Cerebral edema leading to brain herniation (CRS was ongoing)	The subject had encephalopathy (Day 5 to Day 8), hypoxia (Day 5 to Day 8), seizure (Day 5 to Day 6), brain edema (Day 6 to Day 8), hypotension (Day 6 to Day 8), brain herniation (Day 7 to Day 8). Grade 4 CRS (Day 5 to Day 8)
(b) (6)	72	AE	Sepsis in setting of PD	The subject had bacteremia (Day 21 to Day 26), escherichia sepsis (Day 40 to Day 71), osteomyelitis fungal (Day 45 to Day 72), sepsis (Day 72). This subject did not respond to KTE-X19 as of Day 16 (dataset ADEFF.xpt) and started another anticancer therapy (hyper-CVAD from Day 22 to Day 32, dataset ADCM.xpt) prior to this fatal event.
(b) (6)	15	AE	Fungal pneumonia (CRS was ongoing)	The subject had Grade 3 CRS (Day 0 to Day 15), Dyspena on Day 0, Hypoxia (Day 0 to Day 4),

Subject ID	Day of Death	Applicant Cause of Death	FDA Adjudicated Root Cause of Death	FDA Comments
				tachycardia (Day 0 to Day 1), febrile neutropenia (Day 10 to Day 11), pneumonia (Day 15). Received Oxygen, Toci (on Day 1). IL6 increased by 6 folds from baseline on Day 0, by 25 folds on Day 7. and by 46 folds by Day 14. IFNG Increased by ~7 folds on Day 7 and 4.6 folds on Day 14. Past medical history included fungal (aspergillas) pneumonia. Additional information was later provided by the site indicating a lung infection on Day 10 based on CT. Despite being recommended escalated care, the subject requested discharge to home hospice care, and ultimately had a fatal outcome. Per the MedWatch form: CRS resolved by Day 4. The reviewer concluded that CRS may have been ongoing at the time of death.
(b) (6)	46	AE	Fungal pneumonia in setting of PD	The subject had fungal pneumonia (Day 4 to Day 46). This subject relapsed on Day 4 (Circulating lymphoblasts was 90% on Day 4) and received another anticancer therapy (inotuzumab from Day 10 to Day 39) prior to this fatal event.
(b) (6)	491	AE	Respiratory failure in setting of PD	The subject had respiratory failure (Day 490 to Day 491). This subject relapsed on Day 314 after an initial response to KTE-X19 and had received 2 subsequent lines of therapy with TKIs.
(b) (6)	18	AE	Sepsis	The subject had cellulitis and septic shock with pseudomonas aeruginosa (Day 15 to Day 18)

Source: FDA Analysis. ADSLFDA, ADAEFDA, ADCRSFDA, ADNEFDA, ADEFFFDA, ADCYTO. Narratives, Case Report Forms
Abbreviations: AE: Adverse event; Allo SCT: Allogenic stem cell transplant; CRS: Cytokine Release Syndrome; DIC: Disseminated intravascular coagulation; HSV: Herpes simplex virus; PD: Progressive disease

Reviewer comment: *The Applicant stated that the cause of death was due to AEs in eight subjects and due to "other = DIC" in one subject. Five of these subjects AE terms were ALL, therefore these subjects' deaths were considered by the Reviewer to be due to PD and not due to AE.*

Not including AEs in setting of PD, five (6%) subjects died due to AEs: one (1%) subject with cerebral edema, four (5%) subjects with infections (sepsis, fungal pneumonia, and HSV viremia). The Reviewer recommends to not include the Grade 5 HSV viremia as an adverse drug reaction in the label because it occurred post-allo SCT on Day 309 and was deemed unrelated to KT-X19. Therefore, the incidence of fatal adverse reaction in the label will be reported as 5% (four deaths: one due cerebral edema and three due to infections). Notably, of the 4 subjects who had fatal adverse reactions: one subject with fatal pneumonia had pre-existing pneumonia prior to study enrollment, and one subject with fatal sepsis had prolonged cytopenia and immunosuppression from prior therapies and underlying disease (ANC = 200 and Platelets = 9 at time of leukapheresis and ongoing until the time of death on Day 50).

Note that although there were no Grade 5 CRS reported, however, CRS symptoms were ongoing at the time of death in three subjects.

Serious Adverse Events

Data:

Among the 55 subjects treated in Phase 2, 41 subjects (75%) had SAEs; the most common were hypotension (29%), pyrexia (27%), and hypoxia (13%). The most common worst Grade 3 or higher SAEs were hypotension (24%), hypoxia (13%), and pyrexia (11%). The most common worst Grade 3 or higher SAEs that were deemed related to KTE-X19 were hypotension (24%), hypoxia (13%) and pyrexia (11%). Additional information is provided in m5.3.5.2, ZUMA-3, Primary Analysis CSR, Section 11.2.7, Table 54; ADSL, ADAE.

In the combined studies ZUMA-2 and ZUMA-18, 69 subjects (67%) had SAEs; the most common were pyrexia (17%), encephalopathy (17%), and hypotension (14%). The most common worst Grade 3 or higher SAEs were encephalopathy (16%), pneumonia (12%), and hypotension (11%). The most common worst Grade 3 or higher SAEs related to KTE-X19 were encephalopathy (16%), hypotension (10%), and confusional state and pneumonia (7% each). In ZUMA-4, 6 subjects (72%) had SAEs; the most common were pyrexia and hypotension (33% each); and encephalopathy, confusional state, and tachycardia (14% each). The most common worst Grade 3 or higher SAEs were hypotension (31%), encephalopathy (8%), and sepsis and brain oedema (6% each). The most common worst Grade 3 or higher SAEs related to KTE-X19 were hypotension (31%), encephalopathy (8%), and brain oedema (6%). In ZUMA-8, 6 subjects (67%) had SAEs. The only SAE that occurred in ≥ 1 subject was pyrexia (33%). Additional

information is provided in m2.7.4, ZUMA-3 Summary of Clinical Safety, Section 2.2.4; ADSL, ADAE.

The FDA's Assessment:

An SAE was defined as an AE that met at least one of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An AE met the criterion of "requires hospitalization" if the event necessitated an admission to a care facility (e.g., overnight stay). Events that required an escalation of care when the subject was already hospitalized were to be recorded as an SAE. Thus, only a subset of events that met the definition of serious adverse events from within the treatment emergent events are reported in the table below.

Among 78 subjects in the safety analysis set, SAEs occurred in 62 (79%) subjects. Most common SAEs that occurred in ≥ 2 of subjects were CRS, febrile neutropenia (35%), hypotension (32%), encephalopathy (24%), fever (24%), Infections with pathogen unspecified (17%), hypoxia (13%), tachycardia (12%), bacterial infection (6%), respiratory failure (5%), seizure (5%), diarrhea (4%), dyspnea (4%), fungal infection (4%), viral infection (4%), coagulopathy (3%), delirium (3%), fatigue (3%), HLH (3%), musculoskeletal pain (3%), edema, (3%), and paraparesis (3%). See Table 29 for details.

Table 29 FDA - ZUMA-3: Serious Treatment-Emergent Adverse Events (SAE) Occurring in ≥ 1% of the Safety Analysis Set

SAE	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Any SAE	21 (91)	21 (91)	41 (75)	40 (73)	62 (79)	61 (78)
Febrile neutropenia*	11 (48)	11 (48)	27 (35)	27 (35)	27 (35)	27 (35)
Encephalopathy	11 (48)	10 (43)	8 (15)	6 (11)	19 (24)	16 (21)
Hypotension	9 (39)	6 (26)	16 (29)	13 (24)	25 (32)	19 (24)

SAE	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Infections - pathogen unspecified	6 (26)	6 (26)	7 (13)	6 (11)	13 (17)	12 (15)
Fever	4 (17)	4 (17)	15 (27)	6 (11)	19 (24)	10 (13)
Tachycardia	4 (17)	1 (4.3)	5 (9)	0	9 (12)	1 (1.3)
Bacterial infection	3 (13)	3 (13)	2 (3.6)	1 (1.8)	5 (6)	4 (5)
Hypoxia	3 (13)	2 (9)	7 (13)	7 (13)	10 (13)	9 (12)
Encephalopathy	2 (9)	0	3 (5)	1 (1.8)	5 (6)	1 (1.3)
Respiratory failure	1 (4.3)	1 (4.3)	3 (5)	3 (5)	4 (5)	4 (5)
Seizure	1 (4.3)	1 (4.3)	3 (5)	2 (3.6)	4 (5)	3 (3.8)
Diarrhoea	1 (4.3)	1 (4.3)	2 (3.6)	2 (3.6)	3 (3.8)	3 (3.8)
Viral infection	1 (4.3)	1 (4.3)	2 (3.6)	2 (3.6)	3 (3.8)	3 (3.8)
Musculoskeletal pain	1 (4.3)	1 (4.3)	1 (1.8)	1 (1.8)	2 (2.6)	2 (2.6)
Delirium	1 (4.3)	1 (4.3)	1 (1.8)	1 (1.8)	2 (2.6)	2 (2.6)
Coagulopathy	1 (4.3)	1 (4.3)	1 (1.8)	0	2 (2.6)	1 (1.3)
Ileus	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Oedema	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Dizziness	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Headache	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Restlessness	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Renal impairment	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Haemorrhage	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Tachypnoea	1 (4.3)	1 (4.3)	0	0	1 (1.3)	1 (1.3)
Chills	1 (4.3)	0	0	0	1 (1.3)	0
Graft versus host disease	1 (4.3)	0	0	0	1 (1.3)	0
Carcinoma in situ	1 (4.3)	0	0	0	1 (1.3)	0
Thrombosis	1 (4.3)	0	0	0	1 (1.3)	0
Fungal infection	0	0	3 (5)	3 (5)	3 (3.8)	3 (3.8)
Dyspnoea	0	0	3 (5)	1 (1.8)	3 (3.8)	1 (1.3)

SAE	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Haemophagocytic lymphohistiocytosis	0	0	2 (3.6)	2 (3.6)	2 (2.6)	2 (2.6)
Paraparesis	0	0	2 (3.6)	2 (3.6)	2 (2.6)	2 (2.6)
Fatigue	0	0	2 (3.6)	0	2 (2.6)	0
Cytopenia	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Neutropenia	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Pancytopenia	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Oedema	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Drug hypersensitivity	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Brain herniation	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Thrombocytopenia	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Brain oedema	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Cauda equina syndrome	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Monoplegia	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Gastritis	0	0	1 (1.8)	0	1 (1.3)	0
Hypoaesthesia oral	0	0	1 (1.8)	0	1 (1.3)	0
Oedema	0	0	1 (1.8)	0	1 (1.3)	0
Hypogammaglobulinaemia	0	0	1 (1.8)	0	1 (1.3)	0
Facial paralysis	0	0	1 (1.8)	0	1 (1.3)	0
Rash	0	0	1 (1.8)	0	1 (1.3)	0

Source: FDA Analysis. ADSLFDA, ADAEFDA
*febrile neutropenia includes events of 'febrile neutropenia' and the overlapping events of 'fever' and 'neutropenia'
Note: Acute lymphocytic leukaemia terms are excluded from the AE analysis

Reviewer comment: *Higher SAEs were observed in subjects with ALL compared to subjects with MCL (79% in ALL vs. 66% in MCL). The SAEs in general were similar across both indications except for seizures which occurred only in subjects with ALL.*

The Applicant reported the AE of febrile neutropenia only in 11 subjects. However, the Reviewer

noted that several subjects had fever that overlapped (within the same time period) with neutropenia (i.e., ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour). The Reviewer identified 16 additional subjects who had overlapping AEs of fever and neutropenia but who were not included in the Applicant's incidence of febrile neutropenia (since it was at the discretion of the investigator to assess whether fever should be reported as febrile neutropenia). Therefore, FDA's analysis of febrile neutropenia included the 11 subjects identified by the Applicant in addition to the 16 subjects identified by FDA, for total of 27 subjects (35%).

Although the majority of the individual AEs of fever or neutropenia were Grades 1-2, febrile neutropenia was graded by the Reviewer as Grade 3 since per the Common Terminology Criteria for Adverse Events CTCAE V5.0, the lowest grade for febrile neutropenia is Grade 3. Because subjects with febrile neutropenia are hospitalized, these events were considered SAEs.

Note that in the ADAEFDA updated dataset, the FDA GT hypotension included erroneously the preferred term (PT) hypertension. The Reviewer reanalyzed the incidence of hypotension and hypertension thought the memo to ensure accuracy.

Treatment Emergent Adverse Events and Adverse Reactions

Data:
An overall summary of AEs in ZUMA-3 is provided in Table .

Table 30 Kite - ZUMA-3 Overall Summary of AEs (Phase 2, Safety Analysis Set)

	Phase2 (N = 55)
Any TEAE	55 (100)
Worst Grade 5	10 (18)
Worst Grade ≥ 3	52 (95)
Any serious TEAE	41 (75)
Worst Grade 5	10 (18)
Worst Grade ≥ 3	40 (73)
Any KTE-X19 related TEAE	51 (93)
Worst Grade 5	2 (4)
Worst Grade ≥ 3	49 (89)
Any serious KTE-X19 related TEAE	34 (62)
Worst Grade 5	2 (4)
Worst Grade ≥ 3	31 (56)
Any TE CRS	49 (89)
Worst Grade 5	0 (0)

	Phase2 (N = 55)
Worst Grade ≥ 3	13 (24)
Any TE neurologic event [a]	33 (60)
Worst Grade 5	1 (2)
Worst Grade ≥ 3	14 (25)
Any TE CRS or neurologic event [a]	50 (91)
Worst Grade 5	1 (2)
Worst Grade ≥ 3	24 (44)
Any serious TE neurologic event [a]	14 (25)
Worst Grade 5	1 (2)
Worst Grade ≥ 3	11 (20)
Any TE neurologic event by SOC [b]	45 (82)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	15 (27)
Any serious TE neurologic event by SOC [b]	14 (25)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	12 (22)
Any TE thrombocytopenia	27 (49)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	24 (44)
Any TE neutropenia	27 (49)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	27 (49)
Any TE anemia	29 (53)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	27 (49)
Any TE infection	20 (36)
Worst Grade 5	4 (7)
Worst Grade ≥ 3	14 (25)
Any serious TE infection	11 (20)
Worst Grade 5	4 (7)
Worst Grade ≥ 3	9 (16)
Any COVID-19 associated TE viral infection	0 (0)
Any non-COVID-19 associated TE viral infection	2 (4)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	2 (4)
Any hypogammaglobulinemia	4 (7)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	0 (0)

	Phase2 (N = 55)
Any tumor lysis syndrome	1 (2)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	1 (2)
Any graft-versus-host disease	1 (2)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	0 (0)

Data cutoff date = 09Sep2020.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; SOC, System Organ Class; TE, treatment emergent; TEAE, treatment-emergent adverse event.
TEAEs include all AEs with an onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with KTE-X19, the AEs occurring during the retreatment period are not included.
Subjects were summarized at their highest grade per CTCAE version 4.03.
CRS is graded per the revised grading system proposed by Lee et al {Lee 2014}.
a. Neurologic adverse events were identified based on a modification of criteria proposed by Topp et al {Topp 2015}.
b Neurologic events were identified based on the MedDRA System Organ Classes of psychiatric disorders and nervous system disorders; excluding 2 high-level group terms: sleep disorders and disturbances, sleep disturbances (incl subtypes); and adding the following 7 preferred terms: tinnitus, papilloedema, diplopia, vision blurred, paraesthesia oral, gait disturbance and nerve injury.
Source: m5.3.5.2, ZUMA-3 Primary Analysis CSR, Table 14.3.1.1.1, ADSL, ADAE

Events considered ADRs for KTE-X19 in the B-ALL population are based on a review of all AEs in ZUMA-3. Symptoms of CRS were captured in the incidence of their respective ADRs as well as in the incidence of CRS. Frequencies of ADRs for anemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin increased, blood uric acid increased, direct bilirubin increased, hypocalcemia, hypokalemia, hyponatremia, hyperglycemia, hypoalbuminemia, and hypophosphatemia were calculated using the laboratory values (m2.5, ZUMA-3 Clinical Overview, Table 8; ADSL, ADAE, ADLB).

An overall summary of AEs in the 4 supporting safety studies is provided in m2.7.4, ZUMA-3 Summary of Clinical Safety, Section 2.2.2, Table 28; ADSL, ADAE.

The Applicant's Position:
Risks associated with KTE-X19 have been well-characterized and no new safety signals were identified relative to those observed in patients with r/r MCL in ZUMA-2 {Wang 2020}.

The FDA's Assessment:

All 78 subjects (100%) had at least one AE. An overview of all AEs is presented in Table 31. The majority of the maximum toxicity grades were Grade 3 and 4 events. Eight subjects (10%) died of AEs and one subject (1%) died of DIC in setting of PD. AEs leading to death included: Cerebral edema, fungal pneumonia, sepsis, HSV viremia (post allo SCT), and DIC. Majority (four) of these

events occurred in setting of PD. CRS was ongoing at time of death in three subjects, one of whom died of cerebral edema and subsequent brain herniation.

Table 31 FDA - ZUMA-3: Summary of Treatment Emergent Adverse Events (TEAEs) in the Safety Analysis Set

Adverse Events	Safety Analysis Set		
	Phase1 N = 23	Phase2 N = 55	Overall N = 78
All-Grade	23 (100)	55 (100)	78 (100)
Grade 3-5	23 (100)	53 (96)	76 (97)
Grade 1-4	20 (87)	45 (82)	65 (83)
Grade 3-4	20 (87)	43 (78)	63 (81)
Grade 3	2 (9)	9 (16)	11 (14)
Grade 4	18 (78)	34 (62)	52 (67)
Grade 5*	0	4 (7)	4 (5)
SAEs	21 (91)	41 (75)	62 (79)

Source: FDA Analysis. ADSL, ADAEFDA
*See above Section on Deaths: Based on FDA review, eight subjects (10%) died due to AEs (five (6%) subjects died due to AE not in setting of PD)
Abbreviation: SAE: serious adverse event

Reviewer comment: *Several information requests were sent the Applicant to verify and re-adjudicate several AEs. The reviewer requested the resubmission of updated datasets that reflect FDA's review and adjudication and FDA GTs. The Applicant submitted the following datasets on 30 July 2021 under SN 0123 and the updated datasets were used for analysis: ADSLFDA, ADAEFDA, ADCRSFDA, ADNEFDA, and ADSAFFDA). Data structure for these datasets are identical to the original version ADSL, ADAE, ADCRS, ADNE, and ADSAF respectively. The ADAEFDA dataset included a column for FDA GT, flag (record level and subject level) for subjects readjudicated to have treatment-emergent febrile neutropenia and a flag for subjects who had readjudication of AEs grade or duration (e.g., fatal AE, AEs contributing to CRS or NE etc.)*

Overall summary of all TEAEs (based on system organ class (SOC)) occurring in ≥ 10% of subjects is listed in Table 31. Most common AEs of any grade were: fever, CRS, hypotension, encephalopathy, tachycardia, chills, headache, fatigue, musculoskeletal pain, hypoxia, rash, oedema, tremor, infection – pathogen unspecified, constipation, decreased appetite, and vomiting.

Hypogammaglobulinemia (not included in the table below) occurred in 7 (9%) of subjects and was all Grade 1 and 2. None were Grade ≥ 3.

Table 32 FDA - ZUMA-3: Treatment-Emergent Adverse Events (TEAE) by System Organ Class occurring in ≥ 10% of Safety Analysis Set

TEAE[#]	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Any TEAE	23 (100)	23 (100)	55 (100)	53 (96)	78 (100)	76 (97)
Immune system disorders						
Cytokine Release Syndrome	23 (100)	7 (34)	49 (89)	13 (24)	72 (92)	20 (26)
Nervous system disorders						
Encephalopathy	19 (83)	10 (43)	30 (55)	11 (20)	49 (63)	21 (27)
Headache	10 (43)	1 (4.3)	20 (36)	0	30 (38)	1 (1.3)
Tremor	8 (35)	0	15 (27)	1 (1.8)	23 (29)	1 (1.3)
Dizziness	2 (9)	1 (4.3)	8 (15)	0	10 (13)	1 (1.3)
Blood and lymphatic system disorders						
Neutropenia	15 (65)	15 (65)	23 (42)	23 (42)	38 (49)	38 (49)
Anaemia	14 (61)	12 (52)	29 (53)	27 (49)	43 (55)	39 (50)
Thrombocytopenia	12 (52)	11 (48)	27 (49)	24 (44)	39 (50)	35 (45)
Coagulopathy	7 (30)	2 (9)	6 (11)	2 (3.6)	13 (17)	4 (5)
Febrile Neutropenia	11 (48)	11 (48)	27 (35)	27 (35)	27 (35)	27 (35)
Leukopenia	2 (9)	2 (9)	15 (27)	14 (25)	17 (22)	16 (21)
Gastrointestinal disorders						
Diarrhoea	12 (52)	2 (9)	13 (24)	3 (5)	25 (32)	5 (6)
Nausea	11 (48)	1 (4.3)	21 (38)	0	32 (41)	1 (1.3)
Constipation	11 (48)	0	8 (15)	0	19 (24)	0
Vomiting	7 (30)	2 (9)	9 (16)	0	16 (21)	2 (2.6)
Abdominal Pain	5 (22)	0	10 (18)	0	15 (19)	0

TEAE[#]	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Aminotransferase Increased	10 (43)	5 (22)	14 (25)	9 (16)	24 (31)	14 (18)
Metabolism and nutrition disorders						
Hypophosphataemia	13 (57)	11 (48)	15 (27)	11 (20)	28 (36)	22 (28)
Hypokalaemia	11 (48)	0	15 (27)	4 (7)	26 (33)	4 (5)
Decreased Appetite	9 (39)	1 (4.3)	8 (15)	0	17 (22)	1 (1.3)
Hypocalcaemia	8 (35)	2 (9)	9 (16)	4 (7)	17 (22)	6 (8)
Hyperglycaemia	8 (35)	1 (4.3)	8 (15)	6 (11)	16 (21)	7 (9)
Hypomagnesaemia	8 (35)	0	13 (24)	0	21 (27)	0
Hyponatraemia	7 (30)	3 (13)	4 (7)	0	11 (14)	3 (3.8)
Vascular disorders						
Hypotension	17 (74)	10 (43)	37 (67)	16 (29)	54 (69)	26 (33)
Haemorrhage	3 (13)	2 (9)	7 (13)	1 (1.8)	10 (13)	3 (3.8)
Hypertension	3 (13)	2 (9)	7 (13)	3 (5)	10 (13)	5 (6)
General disorders and administration site conditions						
Fever	23 (100)	10 (43)	52 (95)	20 (36)	75 (96)	30 (38)
Chills	13 (57)	0	18 (33)	0	31 (40)	0
Oedema	9 (39)	2 (9)	14 (25)	2 (3.6)	23 (29)	4 (5)
Fatigue	9 (39)	1 (4.3)	20 (36)	0	29 (37)	1 (1.3)
Pain	3 (13)	0	7 (13)	1 (1.8)	10 (13)	1 (1.3)
Cardiac disorders						
Tachycardia	15 (65)	2 (9)	34 (62)	3 (5)	49 (63)	5 (6)
Arrhythmia	5 (22)	0	7 (13)	1 (1.8)	12 (15)	1 (1.3)
Respiratory, thoracic and mediastinal disorders						
Hypoxia	8 (35)	7 (30)	16 (29)	11 (20)	24 (31)	18 (23)

TEAE[#]	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Dyspnoea	3 (13)	0	6 (11)	1 (1.8)	9 (12)	1 (1.3)
Cough	2 (9)	0	7 (13)	0	9 (12)	0
Infections and infestations						
Infections - Pathogen Unspecified	8 (35)	6 (26)	14 (25)	11 (20)	22 (28)	17 (22)
Bacterial Infection	5 (22)	4 (17)	7 (13)	2 (3.6)	12 (15)	6 (8)
Fungal Infection	3 (13)	0	7 (13)	4 (7)	10 (13)	4 (5)
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain	7 (30)	2 (9)	18 (33)	2 (3.6)	25 (32)	4 (5)
Muscular Weakness	5 (22)	0	6 (11)	1 (1.8)	11 (14)	1 (1.3)
Psychiatric disorders						
Delirium	6 (26)	2 (9)	8 (15)	2 (3.6)	14 (18)	4 (5)
Anxiety	5 (22)	0	4 (7)	0	9 (12)	0
Insomnia	3 (13)	0	7 (13)	0	10 (13)	0
Skin and subcutaneous tissue disorders						
Rash	9 (39)	0	15 (27)	0	24 (31)	0

Source: FDA analysis. ADAEFDA, ADSLFDA
*Febrile neutropenia includes febrile neutropenia [11 (14%)] and fever overlapping with neutropenia events [16 (21%)].
[#]This table include laboratory abnormalities that were reported in the ADAEFDA dataset as adverse events. These will not be included in the adverse reaction table of the USPI. Laboratory abnormalities in the USPI will be reported based on the ADLB dataset.
Abbreviation: TEAE: treatment emergent adverse event

Reviewer comment: *The overall AEs noted after KTE-X19 treatment are consistent with those seen for the already approved indication of r/r MCL and with other anti-CD19 CAR-T products and are considered of acceptable severity given subjects' advanced stage of the disease. No new safety signal was observed.*

Although the AEs are presented by SOC, some GTs include more than one SOC. For example: encephalopathy includes nervous system disorders and psychiatric disorders SOCs. We placed these group term AEs under the SOC with most representation in the data for that AE and/or clinically most appropriate (e.g., encephalopathy and dizziness under nervous system disorders SOC).

For analyses of infection by pathogen, we included the grouped term (e.g., bacterial, viral, etc.) which was based on the AE high level group term (AEHLGT).

Infections and cytopenias are also known risks from lymphodepletion chemotherapy and pre-existing conditions as discussed below (in analyses of the conditioning chemotherapy period in the AESI discussion.

Reviewer comments pertinent to the adverse drug reaction (ADR) table of the USPI:

Table 32 above will serve as the basis for the ADR table of the USPI. The laboratory abnormalities incidence will be presented in a separate table that is derived from the ADLB dataset and not from the ADAEFDA dataset since the ADLB is more accurate and will capture all laboratory abnormalities rather than just the ones recorded as AEs.

The Applicant proposed grouping several additional terms such as pain. The Reviewer recommended against grouping these terms since they are too broad to provide meaningful information to the Prescribers.

Other clinically important adverse reactions that occurred in <10% of subjects treated with KTE-X19 include the following:

- *Cardiac disorder: cardiac failure (4%), palpitations (3%)*
- *Eye disorders: visual impairment (9%)*
- *Gastrointestinal disorders: dry mouth (6%), dysphagia (4%), oral pain (1%)*
- *Immune system disorders: hypogammaglobulinemia (9%), hemophagocytic lymphohistiocytosis (4%), drug hypersensitivity (1%)*
- *Infections and infestations: viral infection (6%)*
- *Metabolism and nutrition disorders: dehydration (3%), tumor lysis syndrome (1%)*
- *Musculoskeletal and connective tissue disorders: muscle spasms (4%), musculoskeletal stiffness (3%)*
- *Nervous system disorders: seizure (8%), ataxia (5%), peripheral neuropathy (4%), myoclonus (3%), paraparesis (3%), cauda equina syndrome (1%), cerebral edema and brain herniation (1%), and monoplegia (1%)*
- *Renal and urinary disorders: renal impairment (6%)*
- *Respiratory, thoracic and mediastinal disorders: respiratory failure (9%), pulmonary*

edema (6%), pleural effusion (4%), pneumonitis (4%)

- *Skin and subcutaneous tissue disorders: skin lesion (4%), decubitus ulcer (3%), dry skin (3%), skin ulcer (3%), alopecia (1%), hyperhidrosis (1%), skin hyperpigmentation (1%)*
- *Vascular disorders: thrombosis (4%)*

Reviewer comment: *Drug hypersensitivity occurred in one subject (ID (b) (6)) who had drug hypersensitivity that occurred on Day 2. Another subject (ID (b) (6)) had drug hypersensitivity recorded in the ADAEFDA dataset; however, the lower term for the AE was reported as a reaction to Pentamidine which occurred on Day 129, and therefore this AE was not considered an adverse reaction of drug hypersensitive to KTE-X19.*

The incidence of TEAEs (not organized by SOC) occurring in ≥ 10% of the safety analysis set is presented in Table 33 below. Most common non-laboratory AEs (occurring in ≥ 20% of the safety analysis set) included: fever, CRS, hypotension, encephalopathy, tachycardia, nausea, chills, headache, fatigue, febrile neutropenia, diarrhea, musculoskeletal pain, hypoxia, rash, edema, tremor, infections with pathogen unspecified, constipation, decreased appetite, and vomiting. These AEs will be listed in the Highlights Section of the USPI. Most common Grade 3 or 4 TEAEs included: fever, febrile neutropenia, hypotension, encephalopathy, CRS, hypoxia, and infection with pathogen unspecified.

Table 33: FDA - ZUMA-3: Treatment-Emergent Adverse Events (TEAE) in ≥ 10% of Safety Analysis Set

TEAE*	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Any grouped term	23 (100)	23 (100)	55 (100)	53 (96)	78 (100)	76 (97)
Fever	23 (100)	10 (43)	52 (95)	20 (36)	75 (96)	30 (38)
Cytokine Release Syndrome	23 (100)	7 (34)	49 (89)	13 (24)	72 (92)	20 (26)
Hypotension	17 (74)	10 (43)	37 (67)	16 (29)	54 (69)	26 (33)
Encephalopathy	19 (83)	10 (43)	30 (55)	11 (20)	49 (63)	21 (27)
Tachycardia	15 (65)	2 (9)	34 (62)	3 (5)	49 (63)	5 (6)
Anaemia	14 (61)	12 (52)	29 (53)	27 (49)	43 (55)	39 (50)
Thrombocytopenia	12 (52)	11 (48)	27 (49)	24 (44)	39 (50)	35 (45)
Neutropenia	15 (65)	15 (65)	23 (42)	23 (42)	38 (49)	38 (49)
Nausea	11 (48)	1 (4.3)	21 (38)	0	32 (41)	1 (1.3)

TEAE*	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Chills	13 (57)	0	18 (33)	0	31 (40)	0
Headache	10 (43)	1 (4.3)	20 (36)	0	30 (38)	1 (1.3)
Hypophosphataemia	13 (57)	11 (48)	15 (27)	11 (20)	28 (36)	22 (28)
Fatigue	9 (39)	1 (4.3)	20 (36)	0	29 (37)	1 (1.3)
Febrile Neutropenia	11 (48)	11 (48)	27 (35)	27 (35)	27 (35)	27 (35)
Hypokalaemia	11 (48)	0	15 (27)	4 (7)	26 (33)	4 (5)
Diarrhoea	12 (52)	2 (9)	13 (24)	3 (5)	25 (32)	5 (6)
Musculoskeletal Pain	7 (30)	2 (9)	18 (33)	2 (3.6)	25 (32)	4 (5)
Amenotransferase Increased	10 (43)	5 (22)	14 (25)	9 (16)	24 (31)	14 (18)
Hypoxia	8 (35)	7 (30)	16 (29)	11 (20)	24 (31)	18 (23)
Rash	9 (39)	0	15 (27)	0	24 (31)	0
Oedema	9 (39)	2 (9)	14 (25)	2 (3.6)	23 (29)	4 (5)
Tremor	8 (35)	0	15 (27)	1 (1.8)	23 (29)	1 (1.3)
Infections - Pathogen Unspecified	8 (35)	6 (26)	14 (25)	11 (20)	22 (28)	17 (22)
Hypomagnesaemia	8 (35)	0	13 (24)	0	21 (27)	0
Constipation	11 (48)	0	8 (15)	0	19 (24)	0
Decreased Appetite	9 (39)	1 (4.3)	8 (15)	0	17 (22)	1 (1.3)
Hypocalcaemia	8 (35)	2 (9)	9 (16)	4 (7)	17 (22)	6 (8)
Hyperglycaemia	8 (35)	1 (4.3)	8 (15)	6 (11)	16 (21)	7 (9)
Leukopenia	2 (9)	2 (9)	15 (27)	14 (25)	17 (22)	16 (21)
Vomiting	7 (30)	2 (9)	9 (16)	0	16 (21)	2 (2.6)
Abdominal Pain	5 (22)	0	10 (18)	0	15 (19)	0
Delirium	6 (26)	2 (9)	8 (15)	2 (3.6)	14 (18)	4 (5)
Coagulopathy	7 (30)	2 (9)	6 (11)	2 (3.6)	13 (17)	4 (5)
Arrhythmia	5 (22)	0	7 (13)	1 (1.8)	12 (15)	1 (1.3)
Bacterial Infection	5 (22)	4 (17)	7 (13)	2 (3.6)	12 (15)	6 (8)
Hyponatraemia	7 (30)	3 (13)	4 (7)	0	11 (14)	3 (3.8)

TEAE*	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Muscular Weakness	5 (22)	0	6 (11)	1 (1.8)	11 (14)	1 (1.3)
Dizziness	2 (9)	1 (4.3)	8 (15)	0	10 (13)	1 (1.3)
Fungal Infection	3 (13)	0	7 (13)	4 (7)	10 (13)	4 (5)
Haemorrhage	3 (13)	2 (9)	7 (13)	1 (1.8)	10 (13)	3 (3.8)
Hypertension	3 (13)	2 (9)	7 (13)	3 (5)	10 (13)	5 (6)
Insomnia	3 (13)	0	7 (13)	0	10 (13)	0
Pain	3 (13)	0	7 (13)	1 (1.8)	10 (13)	1 (1.3)
Anxiety	5 (22)	0	4 (7)	0	9 (12)	0
Cough	2 (9)	0	7 (13)	0	9 (12)	0
Dyspnoea	3 (13)	0	6 (11)	1 (1.8)	9 (12)	1 (1.3)

Source: FDA Analysis. ADSLFDA, ADAEFDA
Abbreviation: TEAE = treatment-emergent adverse event
*See FDA grouped terms in Section 17.5 Table 58 (Appendix)

Reviewer comment: *Per protocol; subjects must have no evidence of active infection, such as a fever ≥ 38˚C for at least 48 hours prior to commencement of conditioning chemotherapy or prior to investigational product (IP) infusion. The protocol also states that if fever is present within 48 hours prior to product infusion, a call must be made to the Kite medical monitor before proceeding with the KTE-X19 infusion. If an AE grade worsened after IP infusion (e.g., hypotension was Grade 2 during conditioning chemotherapy period and became Grade 3 after IP infusion, then the AE would be considered a treatment emergent AE. Therefore, the AEs in the leukapheresis, conditioning chemotherapy periods are separate from the treatment emergent AEs from the tables below.*

A separate analysis was performed to identify the incidence of AEs during the leukapheresis and conditioning chemotherapy periods respectively. See details below.

Leukapheresis period:

This period was defined from the day of leukapheresis until the day before the start of conditioning chemotherapy for subjects intended to receive KTE-X19 at a dose of 1 x 10^6 cells per Kg. The leukapheresis population included 99 subjects (28 subjects from Phase 1 and 71

subjects from Phase 2). Grade ≥ 3 AEs occurred in 72 (73%) subjects. See Table 34. Most common AEs included anemia, thrombocytopenia, and fever. As noted above in the description of deaths; one subject developed hemiparesis due to air embolism following leukapheresis, rendering this subject ineligible for the study.

Table 34 FDA - ZUMA-3: Summary of Major Adverse Events During Leukapheresis Period

AEs	Analysis population		
	Phase1 N = 28	Phase2 N = 71	Overall N = 99
All-Grade AEs	45 (161)	54 (76)	99 (100)
Grade 3-5 AEs	32 (114)	40 (56)	72 (73)
AEs leading to death	0	0	0
All grade SAEs	20 (71)	19 (27)	39 (39)
Grade 3-5 SAEs	17 (61)	13 (18)	30 (30)

Source: FDA Analysis. ADSLFDA, ADAEFDA

Conditioning Chemotherapy (CC) period:

This period was defined from the first day of CC administration until Day -1 (the day prior to KTE-X19 infusion). The CC population included 82 subjects (25 subjects from Phase 1 and 57 subjects from Phase 2). Any Grade AE occurred in 66 (80%) subjects and Grade ≥ 3 AEs occurred in 39 (48%) subjects. See Table 35. Most common AEs included anemia, nausea, fever, thrombocytopenia, fatigue, neutropenia, diarrhea, vomiting, febrile neutropenia, and headache.

Table 35 FDA - ZUMA-3: Summary of Major Adverse Events During Conditioning Chemotherapy Period

AEs	Analysis population		
	Phase1 N = 25	Phase2 N = 57	Overall N = 82
All-Grade AEs	21 (84)	45 (79)	66 (80)
Grade 3-5 AEs	9 (36)	30 (53)	39 (48)
AEs leading to death	0	0	0
All grade SAEs	3 (12)	8 (14)	11 (13)
Grade 3-5 SAEs	2 (8)	6 (11)	8 (10)

Source: FDA Analysis. ADSLFDA, ADAEFDA

Reviewer comment: *As expected, increased AEs that are related to chemotherapy side effects such as nausea, vomiting, fatigue, diarrhea and cytopenia was observed in the conditioning chemotherapy period.*

Bridging chemotherapy period:

After leukapheresis, bridging therapy was administered to subjects while awaiting product manufacturing, at the discretion of the treating investigator. Most subjects (94%) received bridging therapy. The most administered therapies were dexamethasone, vincristine, and cytarabine. Table 36 provides a summary of AEs in subjects who received and did not receive bridging therapy.

Table 36 FDA - ZUMA-3: Summary of Major Adverse Events During Bridging Therapy Period

AEs	Analysis population				
	Phase1 Bridging N = 22	**Phase1 No bridging N = 1**	**Phase2 Bridging N = 51**	**Phase2 No bridging N = 4**	**Overall N = 78**
All-Grade AEs	22 (100)	1 (100)	51 (100)	4 (100)	78 (100)
Grade 3-5 AEs	22 (100)	1 (100)	49 (96)	4 (100)	76 (97)
AEs leading to death	3 (14)	0	10 (20)	0	13 (17)
All grade SAEs	21 (95)	0	39 (76)	2 (50)	62 (79)
Grade 3-5 SAEs	21 (95)	0	38 (75)	2 (50)	61 (78)
All grade CRS	22 (100)	1 (100)	45 (88)	4 (100)	72 (92)
Grade 3-5 CRS	17 (77)	1 (100)	33 (65)	2 (50)	53 (68)
All grade NE	22 (100)	1 (100)	42 (82)	3 (75)	68 (87)
Grade 3-5 NE	12 (55)	0	14 (27)	1 (25)	27 (35)

Source: FDA Analysis. ADSLFDA, ADAEFDA

Reviewer comment*: Because of the small number of subjects who did not receive bridging therapy, detailed analysis to compare these subjects to those who received it was not performed. However, it appears that the overall safety profile of subjects who received bridging therapy was similar to those who did not.*

Retreatment period:

Subjects were permitted to receive one additional KTE-X19 infusion provided the subject achieved remission of leukemia at their Month 3 or later disease assessment following the initial KTE-X19 infusion and subsequently progressed. Subject must not have had a grade ≥ 2 KTE-X19-related immediate hypersensitivity reaction or grade 4 CRS, grade 4 neurologic events, or any grade of brain edema with the first KTE-X19 infusion.

There were two subjects in the safety analysis population who received one additional dose of KET-X19. Both subjects were from Phase 2. See Table 37 for details. CRS occurred in one subject and no subjects experienced Grade ≥ 3 CRS or any grade NT.

Three additional subjects from Phase 1 (not include in the safety analysis set) were also retreated. CRS occurred in two subjects (no Grade ≥ 3 CRS) and NT in two subjects (One with Grade 3 NT).

Table 37 FDA - ZUMA-3: Summary of Major Adverse Events Occurring After KTE-X19 Retreatment

AEs	Analysis population	
	Phase2 N = 2	Overall N = 2
All-Grade AEs	1 (50)	1 (50)
Grade 3-5 AEs	1 (50)	1 (50)
AEs leading to death	1 (50)	1 (50)
All grade SAEs	1 (50)	1 (50)
Grade 3-5 SAEs	1 (50)	1 (50)
All grade CRS	1 (50)	1 (50)
Grade 3-5 CRS	0	0
All grade NT	0	0
Grade 3-5 NT	0	0

Source: FDA Analysis. ADSLFDA, ADAEFDA, ADCRSFDA, ADNEFDA
Abbreviations: AE = Adverse event, NT = Neurotoxicity

Reviewer comment: *in depth analysis of CRS and NEs in the retreatment period was not performed due to the small number of subjects receiving retreatment and since the primary analysis per protocol did not include the retreatment period. Thus, the analyses will not be included in the label.*

Adverse Events of Special Interest (AESI)

Cytokine Release Syndrome (CRS)

Data:

Among the 55 treated subjects in Phase 2, 89% had CRS, and 24% had worst Grade 3 or higher CRS. The most common worst Grade 3 or higher CRS symptoms were pyrexia (39%), hypotension (33%), and hypoxia (22%). The median time to onset for the first event was 5 days (range: 1 to 12 days) after KTE-X19 infusion. As of the data cutoff date, CRS had solved in 46 of 49 subjects; for the remaining 3 subjects, CRS was ongoing at the time of death. The median duration of CRS was 7.5 days (range: 2 to 48 days) (m5.3.5.2, ZUMA 3 Primary Analysis CSR, Section 11.2.8.1.1.1; ADSL, ADAE, ADSAF).

The FDA's Assessment:

CRS was graded based on the modified Lee 2014 criteria and the CRS events were graded using the CTCAE criteria. Among 78 subjects in the safety analysis set, CRS occurred in 72 subjects (92%), including ≥ Grade 3 (severe, life threatening or fatal) in 26% of subjects. See Table 38. Among subjects who died after receiving KTE-X19, three subjects died while CRS was ongoing; one of whom died of cerebral edema.

Table 38 FDA - ZUMA-3: Incidence of CRS by Toxicity Grade

Worst CRS Toxicity Grade*	Phase1 N = 23 n (%)	Phase2 N = 55 n (%)	Overall N = 78 n (%)
CRS Any Grade	23 (100)	49 (89)	72 (92)
CRS Grade ≥3	7 (30)	13 (24)	20 (26)
Grade 1	4 (17)	11 (20)	15 (19)
Grade 2	12 (52)	25 (45)	37 (47)
Grade 3	6 (26)	7 (13)	13 (17)
Grade 4	1 (4)	6 (11)	7 (9)

Source: FDA Analysis. ADSLFDA, ADCRSFDA
*Using CRS grading by Lee 2014

The median time to onset of CRS was 5 days (range: 1 to 12 days) and the median duration of CRS was 8 days (range: 2 to 63 days). Median time to CRS resolution was 12 days (range: 6 to 63 days). Median time to first Grade ≥ 3 CRS was 7 days (range: 1-15 days). Median time to resolution of Grade ≥ 3 CRS was 12 days (range: 6-29 days). Median duration of Grade ≥ 3 CRS was 5 days (range: 1-23 days). CRS occurred within the first 7 days post KTE-X19 treatment in 70 (90%) subjects.

Key manifestation of CRS occurring in ≥ 10% of subjects included fever, hypotension, tachycardia, headache, chills, hypoxia, fatigue, and nausea. Grade ≥3 events that were associated with CRS and that occurred in >1% of subjects include fever, hypotension, hypoxia, tachycardia, respiratory failure, coagulopathy and HLH. SAEs associated with CRS that occurred in ≥ 2% of subjects included: hypotension, fever, hypoxia, tachycardia, dyspnea, respiratory failure, coagulopathy and fatigue. See Table 39 for details of the individual AEs that were considered part of CRS (All Grades and Grade 3-5).

Table 39 FDA - ZUMA-3: CRS Symptoms in > 1% of the Safety Analysis Set

CRS Symptoms	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Any CRS*	23 (100)	7 (34)	49 (89)	13 (24)	72 (92)	20 (26)
Fever	21 (91)	10 (43)	46 (84)	19 (35)	67 (86)	29 (37)
Hypotension	17 (74)	8 (35)	33 (60)	16 (29)	50 (64)	24 (31)
Tachycardia	15 (65)	2 (9)	30 (55)	3 (5)	45 (58)	5 (6)
Headache	10 (43)	1 (4.3)	20 (36)	0	30 (38)	1 (1.3)
Chills	10 (43)	0	14 (25)	0	24 (31)	0
Hypoxia	5 (22)	5 (22)	14 (25)	11 (20)	19 (24)	16 (21)
Fatigue	3 (13)	0	14 (25)	0	17 (22)	0
Nausea	2 (9)	0	9 (16)	0	11 (14)	0
Tachypnoea	4 (17)	1 (4.3)	1 (1.8)	0	5 (6)	1 (1.3)
Dyspnoea	1 (4.3)	0	3 (5)	1 (1.8)	4 (5)	1 (1.3)
Respiratory failure	1 (4.3)	1 (4.3)	3 (5)	3 (5)	4 (5)	4 (5)
Decreased appetite	1 (4.3)	0	2 (3.6)	0	3 (3.8)	0
Diarrhoea	0	0	3 (5)	1 (1.8)	3 (3.8)	1 (1.3)
Febrile neutropenia[#]	1 (4.3)	1 (4.3)	2 (3.6)	2 (3.6)	3 (3.8)	3 (3.8)
Hyponatraemia	2 (9)	0	1 (1.8)	0	3 (3.8)	0
Blood bilirubin increased	1 (4.3)	1 (4.3)	1 (1.8)	0	2 (2.6)	1 (1.3)
C-reactive protein increased	0	0	2 (3.6)	0	2 (2.6)	0

CRS Symptoms	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Haemophagocytic lymphohistiocytosis	0	0	2 (3.6)	2 (3.6)	2 (2.6)	2 (2.6)
Muscular weakness	1 (4.3)	0	1 (1.8)	0	2 (2.6)	0
Pulmonary oedema	0	0	2 (3.6)	1 (1.8)	2 (2.6)	1 (1.3)
Abdominal distension	0	0	1 (1.8)	0	1 (1.3)	0
Abdominal pain	0	0	1 (1.8)	0	1 (1.3)	0
Distributive shock	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Dizziness	0	0	1 (1.8)	0	1 (1.3)	0
Flushing	0	0	1 (1.8)	0	1 (1.3)	0
Hepatocellular injury	0	0	1 (1.8)	0	1 (1.3)	0
Hyperbilirubinaemia	0	0	1 (1.8)	0	1 (1.3)	0
Hypertriglyceridaemia	1 (4.3)	0	0	0	1 (1.3)	0
Hypophosphataemia	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Musculoskeletal stiffness	1 (4.3)	0	0	0	1 (1.3)	0
Night sweats	1 (4.3)	0	0	0	1 (1.3)	0
Palpitations	0	0	1 (1.8)	0	1 (1.3)	0
Rash	0	0	1 (1.8)	0	1 (1.3)	0
Tinnitus	1 (4.3)	0	0	0	1 (1.3)	0
Tremor	1 (4.3)	0	0	0	1 (1.3)	0
Vomiting	1 (4.3)	0	0	0	1 (1.3)	0

Source: FDA Analysis. ADSLFDA, ADAEFDA, ADCRSFDA
* Lee 2014 grade is used for CRS. All other AEs grading is per CTCAE grade
#Febrile neutropenia doesn't include the FDA adjudicated overlapping AEs of fever and neutropenia

Among 78 subjects in the safety analysis set, 62 subjects (79%) received tocilizumab, 37 of whom received more than one dose (range 1-6 doses). Systemic steroids were used in 40 subjects (41%) subjects for CRS management. Siltuximab (Monoclonal antibody, Interleukin-6 Inhibitor) was used to treat CRS in 3 subjects and NT in 4 subjects, and Anakinra (Interleukin-1

Receptor Antagonist) was used to treat CRS in 4 subjects (one of whom had overlapping NT). See more details in the concomitant medication section in Table 41.

Reviewer comment: *Per Lee et al. 2014, clinical signs and symptoms associated with CRS may include constitutional symptoms (e.g., fever, nausea, fatigue etc..) or other organ toxicities (e.g., cardiovascular, hepatic, renal etc.).*

Our review strategy of finding additional subjects with CRS included identifying fever, hypotension or hypoxia between Day 0 and Day 30 in the subjects who were not flagged as having CRS. We additionally searched for subjects not flagged as having CRS but who received tocilizumab, vasopressors, intravenous fluids (IVF) or oxygen. We did not look for corticosteroid use in subjects not flagged as having CRS given that corticosteroids are used for neurotoxicity as well which is a confounding factor. We also reviewed cytokine and laboratory data (Ferritin, C-reactive protein, IL-6 levels) for supportive evidence. Subjects who were identified to have isolated hypotension without other symptoms suggestive of CRS were not included.

After reviewing all narratives and relevant CRFs and datasets, we did not find any additional subjects as having CRS and all CRS grades were appropriately classified. In addition, the Reviewer did not need to revise the CRS duration.

There was one subject who had Grade 3 HLH and Grade 2 CRS. To be consistent with the review across all CAR T cell products, the Reviewer didn't upgrade the CRS based on HLH grade and kept the two entities separate.

Overall, higher incidence of Grade ≥ 3 CRS was observed in subjects with ALL (26%) compared to subjects with MCL (18%).

Neurologic toxicity

Data:

Among the 55 treated subjects in Phase 2, 60% had at least 1 neurologic AE, and 25% had worst Grade 3 or higher neurologic AEs; 1 subject had a Grade 5 neurologic AE of brain herniation. The most common worst Grade 3 or higher neurologic AEs were aphasia (9%); encephalopathy (7%); and confusional state, agitation, seizure, and paraparesis (each 4%). The median time to onset for the first event was 9 days (range: 2 to 16 days) after KTE-X19 infusion. As of the data cutoff date, neurologic AEs had resolved in 29 of 33 subjects; for the remaining 4 subjects, neurologic AEs were ongoing either at the data cutoff date (1 subject) or at the time of death (3 subjects). The median duration of neurologic AEs was 7 days (range: 1 to 75 days) (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.8.1.2.1; ADSL, ADAE, ADSAF).

The FDA's Assessment:

The Applicant defined neurologic toxicity by two methods. See Section 8.2.3 and 8.2.4. FDA's neurologic toxicity, defined by the Applicant as "Method 2", was based on the MedDRA SOC of psychiatric disorders and nervous system disorders excluding the following high-level group terms (HLGT): sleep disorders and disturbances, and peripheral neuropathies. However, the Reviewer requested that certain AEs under the sleep disorders HLGT such as insomnia when occurring in setting of other neurologic toxicity be included in this definition. In addition, the Reviewer searched for other AEs under other SOCs (e.g., general disorders, eye/ear disorders, respiratory disorders etc.) that were not classified as neurologic toxicity and that overlapped with other neurologic events to see if they need to be included in FDA's neurologic toxicity definition. The information in the USPI is based on FDA's definition and readjudicaton of neurologic toxicity. Grading of neurologic toxicity was per CTCAE criteria.

Among 78 subjects in the safety analysis set, Neurologic toxicity occurred in 68 subjects (87%), including ≥ Grade 3 in 27 subjects (35%). The median time to onset for neurologic events was 7 days (range: 1 to 51 days) with a median duration of 15 days (range: 1 to 397 days). Median time to NE resolution was 22 days (range: 5 to 402 days). Median time to first Grade ≥ 3 neurologic toxicity was 8 days (range: 4-24 days). Median time to resolution of Grade ≥ 3 neurologic toxicity was 22 days (range: 5-402 days). NTs occurred within the first 7 days post KTE-X19 treatment in 43 (55%) subjects.

Six subjects had ongoing neurologic events at the time of death. The onset of neurologic events can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. NT occurred before, during, and after CRS in 4 (5%), 57 (73%), and 8 (10%) of subjects; respectively. Three subjects (4%) had NT without CRS.

The most common neurologic events included Encephalopathy, headache, tremor, delirium, dizziness, insomnia, and anxiety. See Table 40 for details. SAEs occurring in ≥ 2% of subjects included encephalopathy, seizure, delirium, and paraparesis.

Table 40 FDA - ZUMA-3: Neurologic Events in > 1% of the Safety Analysis Set

NE Symptoms	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Any NE	23 (100)	12 (52)	45 (82)	15 (27)	68 (87)	27 (35)
Anxiety	5 (22)	0	4 (7)	0	9 (12)	0

NE Symptoms	Safety Analysis Set					
	Phase1 N = 23		Phase2 N = 55		Overall N = 78	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Ataxia	2 (9)	0	2 (3.6)	0	4 (5)	0
Brain herniation	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Brain oedema	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Cauda equina syndrome	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Delirium	6 (26)	2 (9)	8 (15)	2 (3.6)	14 (18)	4 (5)
Depression	0	0	2 (3.6)	0	2 (2.6)	0
Dizziness	2 (9)	1 (4.3)	8 (15)	0	10 (13)	1 (1.3)
Encephalopathy	19 (83)	10 (43)	30 (55)	11 (20)	49 (63)	21 (27)
Facial paralysis	0	0	1 (1.8)	0	1 (1.3)	0
Headache	10 (43)	1 (4.3)	20 (36)	0	30 (38)	1 (1.3)
Insomnia	3 (13)	0	7 (13)	0	10 (13)	0
Monoplegia	0	0	1 (1.8)	1 (1.8)	1 (1.3)	1 (1.3)
Myoclonus	0	0	2 (3.6)	0	2 (2.6)	0
Paraesthesia	1 (4.3)	0	0	0	1 (1.3)	0
Paraparesis	0	0	2 (3.6)	2 (3.6)	2 (2.6)	2 (2.6)
Restless legs syndrome	0	0	1 (1.8)	0	1 (1.3)	0
Restlessness	2 (9)	2 (9)	0	0	2 (2.6)	2 (2.6)
Seizure	3 (13)	2 (9)	3 (5)	2 (3.6)	6 (8)	4 (5)
Tinnitus	2 (9)	0	0	0	2 (2.6)	0
Tremor	8 (35)	0	15 (27)	1 (1.8)	23 (29)	1 (1.3)

Source: FDA Analysis. ADAEFDA, ADNEFDA
Abbreviation: NE: neurologic event

Reviewer comment: *The Reviewer requested that the Applicant updates the following datasets (ADAEFDA, ADNEFDA, and ADSAFFDA) based on final FDA review and adjudication following several IRs. The Reviewer requested to:*

- *Upgrade the event of Grade 4 brain herniation to Grade 5 (because the AE was fatal), and to add Neurotoxicity Method 2 (FDA) Flag for the Grade 5 brain herniation (the*

Applicant did not Flag this AE because it was under SOC of "Injury poisoning and procedural complications".

- *Add Neurotoxicity Method 2 Flag for the following four subjects who had insomnia that overlapped with other neurologic symptoms:*
  - (b) (6) *: NE duration remained unchanged*
  - (b) (6) *: NE duration in ADNE was changed accordingly to: Day 1 to Day 29 (from Day 6 to Day 26).*
  - (b) (6) *: NE duration remained unchanged*
  - (b) (6) *: NE duration in ADNE was changed accordingly to: Day 0 to Day 7 (from Day 0 to Day 4). The second occurrence of insomnia from Day 22 to Day 37 did not overlap with other NEs.*

Overlap of neurologic toxicity and CRS:

Neurologic toxicity occurred before CRS in 4 (5%) subjects, during CRS in 57 (73%) subjects, and after CRS in 8 (10%) subjects. Three (4%) subjects had NT without CRS.

Reviewer comment: *In Section 5 (Warning and Precautions) of the USPI, when describing the symptoms of CRS and NT for both MCL and ALL indications, there were several AEs that were not grouped in the MCL indication per the GTs used in this application. Therefore, certain AEs (e.g., aphasia, agitation etc.) were ungrouped from the GTs used in this review in order to accurately present the incidence of these AEs across both indications. See Section 8.2.11 for details.*

Overall, the incidence of NT was similar across both population. Specifically, any grade NT was observed in 87% of subjects with ALL and 81% of subjects with MCL, while Grade ≥ 3 NT occurred in 35% of subject with ALL compared to 37% of subjects with MCL.

Concomitant Medications/Procedures

Among 78 subjects in the safety analysis set, 59 subjects (76%) were treated with corticosteroids (with or without tocilizumab), 65 subjects (83%) were treated with tocilizumab (with or without corticosteroids), 55 subjects (71%) were treated with corticosteroids and tocilizumab, 37% were treated with vasopressors, 10% were treated with nonsteroidal immunosuppressive agents other than tocilizumab, and 14% were treated with immunoglobulins. See the Table below. Furthermore, 8 subjects (10%) of subjects had an endotracheal intubation, and 10% of subjects received mechanical ventilation.

Table 41 FDA - ZUMA-3: Concomitant Medications of Interest

	Safety Analysis Set		
Medication	**Phase 1 N=23**	**Phase 2 N=55**	**Overall N=78**
Corticosteroids	18 (78)	41 (75)	59 (76)
Tocilizumab	21 (91)	44 (80)	65 (83)
Corticosteroids or Tocilizumab	21 (91)	48 (87)	69 (88)
Corticosteroids and Tocilizumab	18 (78)	37 (67)	55 (71)
Vasopressors	7 (30)	22 (40)	29 (37)
Nonsteroidal immunosuppressive agents other than tocilizumab*	2 (9)	6 (11)	8 (10)
Immunoglobulin	5 (22)	6 (11)	11 (14)

Source: FDA Analysis. ADCM
* Nonsteroidal immunosuppressive agents other than tocilizumab includes Anakinra and Siltuximab

Reviewer comment: *While the label provides advice regarding the use of tocilizumab and steroids for CRS and NT toxicity management, limited data exist to support any labelling recommendation for the use of alternative inhibitors of IL-6 or other cytokines such as Siltuximab and Anakinra.*

Serious Infections

The Applicant's Position:

Within the SOC of infections and infestations, 25% of subjects in Phase 2 had AEs that were worst Grade 3 or higher; 7% had Grade 5 infections. The most common event by preferred terms was pneumonia (7%). Worst Grade 3 or higher bacterial infections occurred in 4% of subjects. Worst Grade 3 or higher viral infections occurred in 4% of subjects. Worst Grade 3 or higher opportunistic infections occurred in 7% of subjects; 2% had Grade 5 fungal pneumonia. Worst Grade 3 or higher unspecified pathogen infections occurred in 20% of subjects; 5% had Grade 5 events. (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.8.1.4.1; ADSL, ADAE).

The FDA's Assessment:

Infection of any grade occurred in 34 of 78 subjects (44%) and Grade ≥ 3 infections occurred in 23 subjects (30%). Febrile neutropenia was observed in 35% of subjects. This included events of febrile neutropenia (11 subjects (14%)), plus the overlapping events of "fever" and "neutropenia" (16 subjects (21%)). See Table 42.

Table 42 FDA - ZUMA-3: Infections in the Safety Analysis Set

Infections	Safety Analysis Set N=78	
	Grade 1-5 n (%)	Grade 3-5 n (%)
Febrile neutropenia	27 (35)	27 (35)
Infections - Pathogen Unspecified	22 (28)	17 (22)
Pneumonia*	7 (9)	7 (9)
Bacterial Infection	12 (15)	6 (8)
Fungal Infection	10 (13)	4 (5)
Viral Infection	5 (6)	3 (3.8)

Source: FDA Analysis. ADAEFDA
* Pneumonia may be counted more than once. Pneumonia includes: Pneumonia, Pneumonia respiratory syncytial viral, Pneumonia fungal, and Pneumocystis jirovecii pneumonia

Reviewer comment: *Although febrile neutropenia and pneumonia are presented in the table above, they were not included in the incidence of infections and they were rather listed separately to be consistent with the review of the original BLA strategy. Furthermore, although it is useful to categorize infections by pathogens (e.g., bacterial, viral, fungal, unspecified pathogen), in addition, it is important to identify the incidence of common or serious infections sites such as pneumonia. A footnote may be included in the label to indicate that subjects may have been counted more than once when calculating the incidence of pneumonia.*

Serious AEs of infections are presented in Table 43.

Table 43 FDA - ZUMA-3: Serious Infections in the Safety Analysis Set

Serious Infections	Safety Analysis Set N=78 (%)
Febrile neutropenia	27 (35)
Infections - Pathogen Unspecified	13 (17)
Pneumonia*	6 (8)
Bacterial Infection	5 (6)
Fungal Infection	3 (4)
Viral Infection	3 (4)

Source: FDA Analysis. ADAEFDA
*Pneumonia may be counted more than once. Pneumonia includes: Pneumonia, Pneumonia respiratory syncytial viral, Pneumonia fungal, and Pneumocystis jirovecii pneumonia

Hypogammaglobulinemia

The Applicant's Position:

Among the 55 treated subjects in Phase 2, 7% had hypogammaglobulinemia, all of which were worst Grade 1 or worst Grade 2 (each 4%) (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.8.1.5; ADSL, ADAE).

The FDA's Assessment:

Hypogammaglobulinemia occurred in 7 subjects (9%). All were Grade 1 or 2.

Cytopenias

The Applicant's Position:

Among the 55 treated subjects in Phase 2, 44% had worst Grade 3 or higher thrombocytopenia, 49% had worst Grade 3 or higher neutropenia, and 49% had worst Grade 3 or higher anemia. Grade 3 or higher prolonged (ie, present on or after Day 30 following the KTE-X19 infusion on Day 0) neutropenia, thrombocytopenia, or anemia occurred in 25%, 18%, and 7% of subjects, respectively (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.8.1.3.1 ADSL, ADAE).

The FDA's Assessment:

Among 78 subjects in the safety analysis set, Grade 3 or higher cytopenias not resolved by Day 30 following KTE-X19 infusion occurred in 41% of the subjects and included neutropenia (28%), thrombocytopenia (18%), and anemia (13%). Grade 3 or higher prolonged cytopenia not resolved by Day 56 occurred in 18 (23%) subjects and included neutropenia in 12 (15%) subjects, thrombocytopenia in 10 (13%) subjects, and anemia in 6 (8%) subjects.

Seven of the 35 responders (20%) to KTE-X19 had incomplete hematologic recovery by response definition within the first 3 months of KTE-X19 infusion. Four subjects (11%) had Grade 3 or higher prolonged cytopenia by Day 60 and included neutropenia in 3 (9%) subjects and thrombocytopenia in two (6%) subjects. See Table 44 for details.

Table 44 FDA - ZUMA-3: Incidence of Cytopenia in All Responders in the Primary Efficacy Population Lasting through Day 30 and Day 60 after KTE-X19 Treatment

	Incidence of Cytopenia in All Responders (N=35) Lasting Through:	
	Day 30 n (%)	**Day 60 n (%)**
Grade 3 + 4 Cytopenia	7 (20)	4 (11)
Grade 3 Neutropenia	1 (3)	3 (9)
Grade 3 Thrombocytopenia	2 (6)	0
Grade 3 Anemia	0	0
Grade 4 Neutropenia	3 (9)	0
Grade 4 Thrombocytopenia	2 (6)	2 (6)
Grade 4 Anemia	0	0

Source: FDA Analysis. ADAEFDA, ADSLFDA

Additional AESI:

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS):

FDA Assessment

HLH/MAS is an inflammatory reaction that involves the activation of macrophages and T cells. It can be primary or secondary (sometimes associated with viral disease). In the context of CAR T-cell therapy, HLH/MAS has been seen in patients after the CAR T cells are administered.

HLH/MAS occurred in 3 of 78 subjects (4%) (ID (b) (6)) (two of whom had overlapping symptoms of CRS). Two subjects had Grade 3 and one subject had Grade 4 toxicity. Two were considered serious events and no fatal HLH/MAS occurred. The median time to onset for HLH/MAS was 8 days (range: 6 to 9 days) with a median duration of 5 days (range: 2 to 8 days). All three subjects had concurrent events with CRS and NT which may have correlated to the beginning of KTE-X19 cells expansion. Treatment included steroids (in all 3 subjects), etoposide (in 2 subjects), and anakinra (in one subject). No Siltuximab was administered. One subject with Grade 4 underwent plasmapheresis.

Reviewer comment: *HLH/MAS and CRS have overlapping clinical symptoms. HLH/MAS symptoms resolved by Day 12 in all three subjects with adequate treatment. However, the potential risk for this toxicity may be severe and therefore, the Reviewer recommends including*

HLH/MAS as a potential risk in the label in the "Warning and Precautions" (as Section 5.3) and also under "additional important adverse reactions". The Reviewer doesn't recommend including this risk as a box warning given the short duration and non-fatal outcome of these events. Treatment of HLH/MAS warrants a different intervention than that of CRS and should be administered per institutional standards.

Potential Risks

The Applicant's Position:

No secondary malignancies were causally attributed to KTE-X19, no confirmed cases of immunogenicity were identified in Phase 2, and none of the tested subjects were positive for RCR. One subject had Grade 3 nonserious tumor lysis syndrome assessed as related to KTE-X19. One subject had Grade 2 nonserious GVHD assessed as related to KTE-X19; the subjects had undergone allo-SCT prior to enrollment in ZUMA-3 (m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.8.2; ADSL, ADIS, ADAE).

The FDA's Assessment:

Important potential risks associated with KTE-X19 include secondary malignancies, immunogenicity, RCR, tumor lysis syndrome, and GVHD. The incidences of these AEs were as follow:

- GVHD: 4 (5%) subjects
  - 2 subjects developed GVHD post-allo SCT following KTE-X19
  - 2 subject underwent allo SCT prior to enrollment in ZUMA-3 and developed GVHD on Day 39 and Day 51 respectively.
- Tumor lysis syndrome: one subject
- Secondary malignancies: one subject had squamous cell carcinoma, and one subject had Carcinoma in situ which were assessed to be unrelated to KET-X19.
- Immunogenicity: Among all 100 subjects treated with KTE-X19 at any dose, two subjects (both from Phase 1) were confirmed to have antibodies to the anti-CD19 CAR after KTE-X19 infusion. One of these subjects was confirmed to be antibody-positive after retreatment with KTE-X19.
- RCR: Among all 100 subjects treated with KTE-X19 at any dose, 53 (97%) subjects had available samples to test for RCR. No subject tested positive.

Summary

The Applicant's Position:

In ZUMA-3, Grade 3 or higher neutropenia, thrombocytopenia, and anemia occurred in 49%, 44%, and 49% of subjects treated in Phase 2, respectively. Twenty-five percent of subjects in Phase 2 had Grade 3 or higher infections, including 7% with fatal infections. The rates of these identified risks were similar to those observed across different studies and treatment modalities and are consistent with the underlying disease. The overall rates of CRS and neurologic AEs in ZUMA-3 were generally comparable to those observed in ZUMA-2 {Wang 2020}, although a higher incidence of Grade 3 or higher CRS was observed in ZUMA-3. This finding may be attributable to the high disease burden in the majority of subjects enrolled in the study, consistent with previous observations {Park 2018}. CRS and neurologic AEs associated with KTE-X19 treatment mostly occurred in the first month after cell infusion and were largely reversible and manageable with medical intervention.

The FDA's Assessment:

Among the 78 subjects in the safety analysis set:

- The most common adverse reactions (incidence ≥ 20%) included fever, CRS, hypotension, encephalopathy, tachycardias, febrile neutropenia nausea, chills, headache, fatigue, diarrhea, musculoskeletal pain, hypoxia, rash, edema, tremor, infection-pathogen unspecified, hypomagnesemia, constipation, decreased appetite, and vomiting.
- Grade 3 or higher adverse reactions occurred in 76 (97%) subjects.
- Most common Grade 3 or higher AESI included: prolonged cytopenias (47 subjects; 61%), febrile neutropenia (27 subjects; 35%), neurologic toxicities (27 subjects; 35%), infections (23 subjects; 30%), and CRS (20 subjects; 26%).
- Any grade of CRS occurred in 72 (92%) subjects, and neurologic toxicity occurred in 68 (87%) subjects.
- SAEs occurred in 62 (79%) subject and included febrile neutropenia, encephalopathy, fever, CRS, pneumonia, infections-pathogen unspecified, hypoxia, hypotension, fatigue, urinary tract infection, rash, and thrombosis.
- SAEs Grade 3 or higher occurred in 54 (37%) subjects and included hypotension, encephalopathy, fever, Infections with pathogen unspecified, hypoxia, tachycardia, bacterial infection, respiratory failure, seizure, diarrhea, dyspnea, fungal infection, viral infection, coagulopathy, delirium, fatigue, HLH, musculoskeletal pain, edema, and paraparesis.
- Four subjects had fatal adverse reactions: one with cerebral edema and three with infections (sepsis and fungal pneumonia). Three subjects with ALL had ongoing CRS events at the time of death.

Overall, the only new safety signal that was identified in subjects with ALL is the occurrence of HLH/MAS which was not observed in subjects with MCL who received KTE-X19. However, HLH/MAS is a known adverse reaction that has been associated with the same class of CAR T-cell products.

Dropouts and/or Discontinuations Due to Adverse Effects and Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

KTE-X19 is administered as a single infusion. No subject in ZUMA-3 discontinued the infusion due to an AE.

The FDA's Assessment:

The Reviewer agrees.

Laboratory Findings

Data:

The most common worst Grade 3 or higher increased laboratory values in ZUMA-3 in Phase 2 were ALT (31%), AST (25%), and glucose (24%); the most common worst Grade 3 or higher decreased laboratory values were leukocytes (98%), neutrophils (96%), and lymphocytes (95%).

In the combined studies ZUMA-2 and ZUMA-18, the most common worst Grade 3 or higher increased laboratory values were urate (19%), ALT (14%), and AST and glucose (each 12%); the most common worst Grade 3 or higher decreased laboratory values were neutrophils (99%), leukocytes (98%), lymphocytes (97%), and platelets (63%). In ZUMA-4, the most common worst Grade 3 or higher increased laboratory values were bilirubin (17%), urate and direct bilirubin (each 14%), and AST and glucose (each 11%); the most common worst Grade 3 or higher decreased laboratory values were leukocytes and neutrophils (each 100%), lymphocytes (89%), platelets (75%), and hemoglobin (64%). In ZUMA-8, the most common worst Grade 3 or higher increased laboratory values were bilirubin, urate, and calcium (each 11%); the most common worst Grade 3 or higher decreased laboratory values were neutrophils (100%), leukocytes (78%), and lymphocytes (67%).

The FDA's Assessment:

Routine clinical safety assessments included clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations. Specialty tests were conducted for replication competent retrovirus (RCR) and antibodies to KTE-X19.

Toxicity grading was based on CTCAE version 4.03 criteria. The most comment Grade 3 or 4 laboratory abnormalities included: leukopenia, neutropenia, lymphopenia, thrombocytopenia, and anemia. See Table 45 for details.

Note that postKTE-X19 infusion lab toxicity includes lab toxicities observed on or after the KTE-X19 infusion date. While baseline lab assessment is defined as the last value taken prior to the first dose of conditioning chemotherapy.

Table 45 FDA - ZUMA-3: Grade ≥ 3 Laboratory Abnormalities in ≥ 10% of subjects in the Safety Analysis Set

Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set N=78 (%)
Leukopenia	77 (99)
Neutropenia	76 (97)
Lymphopenia	75(96)
Thrombocytopenia	68 (87)
Anemia	60 (77)
Hypophosphatemia	37 (47)
Alanine aminotransferase increased	24 (31)
Aspartate aminotransferase increased	18 (23)
Hyperglycemia	17 (22)
Hypocalcemia	17 (22)
Blood uric acid increased	15 (19)
Direct Bilirubin increase	15 (19)
Hyponatremia	15 (19)
Hypokalemia	10 (13)
Hyperbilirubinemia	8 (10)

Source: FDA Analysis. ADLB, ADSLFDA

Reviewer comment: *The denominators for laboratory analyses in the table above are based on subjects with or without baseline values. In general, two analyses may be done to evaluate the laboratory abnormalities: 1) one where the denominators for laboratory analyses are based on subjects with a baseline and at least one on-study value (i.e., subjects must have had at least one grade worsening on study to be counted in analyses and only worst grade are included in this analysis), and 2) another where the denominator is based off the entire safety population*

regardless of whether or not the subjects had baseline tests. However, the former analysis method may underestimate the true incidence of lab abnormalities in subjects without a baseline assessment. This is more the case for labs that might not routinely be drawn at baseline, such as uric acid etc. A more conservative approach is to assume that abnormal labs occurring after treatment, with a missing baseline grade, are treatment emergent. Therefore, the Reviewer recommends that the labs analyses in the label follow the latter approach.

Vital Signs

The Applicant's Position:

Investigators were to review all vital sign findings. If a clinically significant vital sign abnormality was a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) was to be recorded on the CRF.

The FDA's Assessment:

There was one subject in the safety analysis set (ID (b) (6)) who developed Grade 1 infusion reaction that manifested with epigastric pain, and another subject (ID (b) (6) who had Grade 2 drug hypersensitivity on Day 2 . Overall, in ZUMA-3, the lack of frequent vital sign monitoring immediately after infusion preclude an analysis for infusion-related reactions.

Immunogenicity

The Applicant's Position:

Immunogenicity is an identified potential risk associated with KTE-X19; additional information is provided in Potential Risks.

The FDA's Assessment:

KTE-X19 has the potential to induce anti-product antibodies. The immunogenicity of KTE-X19 was evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. To be confirmed antibody positive, a cell-based confirmatory positive result is required. Among all subjects treated with KTE-X19 at any dose, 16 subjects tested positive for antibodies at any timepoint, based on the initial screening assay in ZUMA-3. Among 12 subjects with evaluable samples for confirmatory testing, two subjects (who were from Phase 1) were confirmed to be antibody-positive after treatment. One of the two subjects had a confirmed positive antibody result at Month 6. The second subject had a confirmed antibody result at retreatment Day 28 and Month 3. None of the subjects who developed antibodies had a hypersensitivity reaction. No subject in the Phase 2 had a positive confirmatory antibody test.

Notably, immunogenicity appears to be numerically higher in subjects with ALL (2 subjects with confirmed antibodies test) compared to subjects with MCL (none). However, this observation is limited by the small sample size.

Hospitalization:
All subjects were hospitalized for a minimum of seven days post KTE-X19 infusion per protocol. All 78 subjects had initial hospitalization of at least seven days per protocol, and 42 (54%) subjects were admitted to the intensive care unit (ICU).

The median duration of initial hospitalization was 24 days with a range of 7 to 151 days. The median duration of ICU stay was 4 days with range of 1 to 25 days. The median duration of hospitalization for the two subjects in the retreatment period was 13 days with a range of 8 to 17 days.

Reviewer comment:
Based on the data from ZUMA-3, the incidence of neurologic events (first occurrence) within the first seven days after KTE-X19 infusion was in 55% (43/78) of subjects. Among the 78 subjects in the safety analysis set, 25 (32%) subjects had onset of neurological symptoms after Day 7 following KTE-X19 treatment (the majority of subjects had onset before Day 15). To ensure subjects safety, The Reviewer recommends revising the daily monitoring requirement following KTE-X19 infusion, in the USPI, from 7 days to 14 days. This is to capture most adverse reactions related to neurologic toxicity and CRS to ensure safe use of KTE-X19.

Thus, the Reviewer recommends that the label inform of the requirement to monitor subjects at the certified healthcare facility daily for at least 14 days following KTE-X19 infusion for signs and symptoms of CRS and NT. This recommendation is based on the requirements in the protocol, the clinical data related to the timing of onset of CRS and neurologic events, and the availability of guidance to treat these serious adverse events. The knowledge of and experience with CAR T cell therapy products have expanded over recent years, and with adequate safety procedures in place, outpatient monitoring is considered acceptable after KTE-X19 infusion.

8.2.5. Analysis of Submission-Specific Safety Issues

AEs of special interest observed in ZUMA-3 are summarized in Section 8.2.4; additional information is in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.8, and m2.7.4 Summary of Clinical Safety provides safety data from ZUMA-3 and supporting KTE-X19 studies.

The Applicant's Position:
No new safety signals were identified relative to those observed in patients with r/r MCL in ZUMA-2.

In ZUMA-3, Grade 3 or higher neutropenia, thrombocytopenia, and anemia occurred in 49%, 44%, and 49% of subjects treated in Phase 2, respectively. Twenty-five percent of subjects treated in Phase 2 had Grade 3 or higher infections, including 7% with fatal infections. The rates of these identified risks were similar to those observed across different studies and treatment modalities and are consistent with the underlying disease. The overall rates of CRS and neurologic AEs in ZUMA 3 were generally comparable to those observed in ZUMA 2 {Wang 2020}, although a higher incidence of Grade 3 or higher CRS was observed in ZUMA 3. This finding may be attributable to the high disease burden in the majority of subjects enrolled in the study, consistent with previous observations {Park 2018}. CRS and neurologic AEs associated with KTE-X19 treatment mostly occurred in the first month after cell infusion and were largely reversible and manageable with medical intervention.

The FDA's Assessment:
The overall safety profile of KTE-X19 in ZUMA-3 was comparable to that of subjects with r/r MCL and no new safety signals were identified relative to those observed in subjects with r/r MCL in ZUMA-2.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees that no information was included in this submission regarding COA to inform safety of KTE-X19.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Subgroup analyses of AEs were performed according to select baseline characteristics, including age, sex, and Eastern Cooperative Oncology Group performance status. Subjects who were ≥ 65 years old had a numerically higher incidence of worst Grade 3 or higher KTE-X19-related AEs, worst Grade 3 or higher KTE-X19-related SAEs, worst Grade 3 or higher neurologic AEs, and worst Grade 3 or higher neutropenia compared with subjects who were < 65 years old. Females had a numerically higher incidence of SAEs, worst Grade 3 or higher SAEs, KTE-X19-related SAEs, and worst Grade 3 or higher KTE-X19-related SAEs compared with males. Subjects who had an ECOG status of 0 had a numerically higher incidence of worst Grade 3 or higher KTE-X19-related AEs, worst Grade 3 or higher neurologic AEs, and worst Grade 3 or higher anemia. Additional details are provided in m5.3.5.2, ZUMA-3 Primary Analysis CSR, Section 11.2.9 (ADSL,

ADAE, ADBASE).

The Applicant's Position:
The subgroup analyses should be interpreted with caution due to the small number of subjects.

The FDA's Assessment:
The following subgroups were used for analysis of TEAEs:

- Age group (< 65 years / ≥ 65 years)
- Gender (male / female)
- Race (White or Caucasian / Black or African American / Asian / American Indian or Alaska Native / Native Hawaiian or Other Pacific Islander)
- Ethnicity (Hispanic or Latino / Non-Hispanic or Latino)

Of the 78 subjects in the safety analysis set, 66 (85%) subjects were < 65 years old and 12 (15%) subjects were 65 years of age or older. Table 46 shows the TEAEs by age group in decreasing order of the difference in incidence between age groups (<65 year old vs ≥ 65 years old). Only TEAE with a risk difference ≥ 10% are shown. Older adults appeared to have more neutropenia, constipation, increased aminotransferases, hypogammaglobulinaemia, dysphagia, encephalopathy, insomnia, pulmonary edema, renal impairment, and bacterial infections compared to younger adults. In addition, compared with subjects who were < 65 years old, subjects who were ≥ 65 years old showed a trend toward a higher incidence of CRS (100% vs. 91%).

Table 46 FDA - ZUMA-3: TEAEs by Age Group in the Safety Analysis Set

	< 65 Years (N = 66)		≥ 65 Years (N = 12)		Risk Difference
TEAE	**n**	**%**	**n**	**%**	**(%)**
Neutropenia	28	42	10	83	-41
Constipation	13	20	6	50	-30
Transaminases increased	18	27	6	50	-23
Hypogammaglobulinaemia	4	6	3	25	-19
Dysphagia	1	2	2	17	-15
Encephalopathy	40	61	9	75	-14
Insomnia	7	11	3	25	-14
Pulmonary oedema	3	5	2	17	-12
Renal impairment	3	5	2	17	-12
Bacterial infection	9	14	3	25	-11
Coagulopathy	12	18	1	8	10
Hypokalaemia	23	35	3	25	10
Thrombocytopenia	34	52	5	42	10
Blood bilirubin increased	7	11	0	0	11
Visual impairment	7	11	0	0	11
Delirium	13	20	1	8	11
Hypomagnesaemia	19	29	2	17	12
Hypotension	52	79	8	67	12
Abdominal pain	14	21	1	8	13
Anxiety	9	14	0	0	14
Dyspnoea	9	14	0	0	14
Infection	20	30	2	17	14
Fatigue	26	39	3	25	14
Haemorrhage	10	15	0	0	15
Oedema	21	32	2	17	15
Tremor	21	32	2	17	15
Febrile neutropenia	11	17	0	0	17
Rash	22	33	2	17	17
Vomiting	16	24	0	0	24
Tachycardia	44	67	5	42	25
Anaemia	39	59	4	33	26
Headache	29	44	1	8	36

Source: FDA Analysis (By MAED). ADAEFDA

Reviewer comment: *Six (50%) subjects who were ≥ 65 years old had ph positive ALL compared to 11 (17%) subjects < 65 years of age. Overall, there were no remarkable differences in baseline characteristics or concomitant medications that would predispose subjects who were ≥ 65 years old to a higher risk of the listed AEs than subjects who were < 65 years old. Furthermore, data from other studies (e.g., ZUMA-18) that enrolled subjects ≥ 65 years of age were submitted only in the ISS dataset. The submission didn't include narratives and details on TEAEs from these studies. Therefore, pooled analysis across these studies was not performed.*

Because of the small number of subjects aged 65 years and older who were treated in ZUMA-3, results should be interpreted with caution. Therefore, The Reviewer doesn't recommend including this observation in Section 8.5 "Geriatric Use" of the USPI.

Table 47, Table 48, and Table 49 include TEAEs by gender, race, and ethnicity respectively.

Table 47 FDA - ZUMA-3: TEAEs by Gender in the Safety Analysis Set

	Male (N = 42)		Female (N = 36)		Risk Difference	
TEAE	**n**	**%**	**n**	**%**	**%**	
Arrhythmia	3		7	9	25	-18
Bacterial infection	3		7	9	25	-18
Hypomagnesaemia	8		19	13	36	-17
Tachypnoea	0		0	6	17	-17
Thrombocytopenia	18		43	21	58	-15
Diarrhoea	11		26	14	39	-13
Oedema	10		24	13	36	-12
Flushing	1		2	5	14	-12
Hypokalaemia	12		29	14	39	-10
Rash	11		26	13	36	-10
Infection	10		24	12	33	-10
Decreased appetite	11		26	6	17	10
Procedural pain	4		10	0	0	10
Visual impairment	6		14	1	3	12
Chills	19		45	12	33	12
Fatigue	18		43	11	31	12
Dizziness	8		19	2	6	13
Hypotension	35		83	25	69	14
Nausea	20		48	12	33	14
Headache	19		45	11	31	15
Cough	9		21	0	0	21

Source: FDA Analysis (By MAED). ADAEFDA

Table 48 FDA - ZUMA-3: TEAEs by Race in ≥ 10% in the Safety Analysis Set

	White (N = 56)		Black or African American (N = 1)		Asian (N = 5)		American Indian or Alaska Native (N = 1)		Native Hawaiian or Other Pacific Islander (N = 1)		Other (N = 10)	
TEAE	n	%	n	%	n	%	n	%	n	%	n	%
Fever	53	95	1		5		1		1		10	100
CRS	51	91	1	100	5	100	1	100	1	100	9	90
Hypotension	41	73	0	0	5	100	1	100	1	100	8	80
Encephalopathy	35	63	0	0	2	40	1	100	1	100	8	80
Tachycardia	33	59	0	0	4	80	1	100	1	100	9	90
Anaemia	32	57	1	100	3	60	0	0	0	0	5	50
Thrombocytopenia	29	52	1	100	3	60	1	100	0	0	3	30
Neutropenia	25	45	0	0	3	60	1	100	1	100	6	60
Fatigue	22	39	1	100	2	40	1	100	0	0	2	20
Nausea	21	38	1	100	4	80	0	0	0	0	5	50
Headache	20	36	1	100	3	60	1	100	0	0	5	50
Chills	20	36	1	100	3	60	1	100	1	100	5	50
Diarrhoea	20	36	0	0	4	80	0	0	0	0	1	10
Hypokalaemia	20	36	0	0	2	40	1	100	0	0	2	20
Hypoxia	20	36	0	0	1	20	1	100	0	0	2	20
Transaminases increased	19	34	0	0	2	40	0	0	0	0	2	20
Tremor	18	32	0	0	1	20	1	100	0	0	3	30
Rash	17	30	1	100	2	40	0	0	0	0	4	40
Oedema	17	30	0	0	2	40	1	100	0	0	3	30
Musculoskeletal pain	16	29	1	100	2	40	1	100	0	0	5	50
Constipation	16	29	0	0	0	0	0	0	1	100	2	20
Hypophosphataemia	16	29	0	0	3	60	1	100	1	100	5	50
Decreased appetite	14	25	0	0	2	40	1	100	0	0	0	0
Leukopenia	14	25	0	0	1	20	0	0	0	0	1	10
Vomiting	14	25	0	0	0	0	0	0	0	0	2	20
Hypomagnesaemia	13	23	1	100	2	40	1	100	1	100	1	10
Infection	13	23	0	0	1	20	1	100	1	100	5	50
Hyperglycaemia	12	21	1	100	2	40	0	0	0	0	1	10
Hypocalcaemia	11	20	0	0	2	40	0	0	1	100	3	30
Abdominal pain	10	18	0	0	3	60	1	100	0	0	1	10
Delirium	10	18	0	0	1	20	0	0	0	0	3	30

Febrile neutropenia	10	18	0	0	1	20	0	0	0	0	0	0
Pain	10	18	0	0	0	0	0	0	0	0	0	0
Haemorrhage	9	16	0	0	1	20	0	0	0	0	0	0
Hyponatraemia	9	16	0	0	1	20	0	0	0	0	1	10
Arrhythmia	8	14	0	0	0	0	1	100	0	0	2	20
Bacterial infection	8	14	0	0	0	0	0	0	0	0	2	20
Coagulopathy	8	14	0	0	1	20	1	100	0	0	3	30
Muscular weakness	8	14	0	0	1	20	0	0	0	0	2	20
Anxiety	7	13	0	0	2	40	0	0	0	0	0	0
Cough	7	13	0	0	1	20	0	0	0	0	1	10
Dizziness	7	13	0	0	1	20	0	0	0	0	2	20
Dyspnoea	7	13	0	0	0	0	0	0	0	0	1	10
Insomnia	7	13	0	0	1	20	1	100	0	0	1	10
Fungal infection	6	11	0	0	2	40	0	0	0	0	2	20
Hypogammaglobulinaemia	6	11	0	0	0	0	0	0	0	0	0	0

Source: FDA Analysis (By MAED). ADAEFDA

Table 49 FDA - ZUMA-3: TEAEs by Ethnicity in the Safety Analysis Set

	Hispanic or Latino (N = 22)		Not Hispanic or Latino (N = 54)		Risk Difference
TEAE	**n**	**%**	**n**	**%**	**%**
Fatigue	4	18	25	46	-28
Hypoxia	4	18	20	37	-19
Decreased appetite	3	14	14	26	-12
Pain	1	5	9	17	-12
Hypogammaglobulinaemia	0	0	6	11	-11
Oropharyngeal pain	0	0	6	11	-11
Oedema	5	23	18	33	-11
Transaminases increased	5	23	18	33	-11
Anxiety	1	5	8	15	-10
Constipation	4	18	15	28	-10
Muscular weakness	5	23	6	11	12
Weight decreased	3	14	1	2	12
Infection	8	36	13	24	12
Visual impairment	4	18	3	6	13
Chills	11	50	20	37	13
Hypermagnesaemia	3	14	0	0	14
Musculoskeletal pain	10	45	15	28	18
Encephalopathy	17	77	32	59	18
Hyponatraemia	6	27	5	9	18
Tachycardia	17	77	32	59	18
Hypotension	20	91	38	70	21
Hypoalbuminaemia	5	23	1	2	21
Rash	11	50	13	24	26
Hypocalcaemia	9	41	8	15	26
Hypophosphataemia	12	55	15	28	27

Source: FDA Analysis (By MAED). ADAEFDA

Reviewer comment: *Overall, analysis of TEAEs across the selected subgroups revealed no remarkable differences in the type or frequency of TEAEs experienced. Evaluation of differences in the incidence of TEAEs was often limited by the relative sizes of the subgroups being compared.*

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific studies were conducted to evaluate safety concerns.

The FDA's Assessment:

Dose-Related Toxicities

In ZUMA-3, there were a total of 100 subjects treated with 3 target dose levels of KTE-X19 (0.5, 1.0 and 2.0 x 10^6 cells/kg). Table 50 shows the incidence of any-grade AE by target KTE-X19 dose in decreasing frequency in the subgroup at the 1.0 x 10^6 cells/kg target level. Only AEs with an incidence of at least 20% are shown.

Table 50 FDA - All Grade TEAEs by Target KTE-X19 Dose in the Safety Population

Adverse Event[a]	0.5 x 10^6 cells/kg N=16		1.0 x 10^6 cells/kg N=78		2.0 x 10^6 cells/kg N=6	
	n	%	n	%	n	%
Fever	11	69	75	96	6	100
Cytokine release syndrome	13	81	72	92	6	100
Hypotension	11	69	60	77	5	83
Encephalopathy	7	44	49	63	5	83
Tachycardia	8	50	49	63	4	67
Anaemia	4	25	43	55	3	50
Thrombocytopenia	7	44	39	50	2	33
Neutropenia	5	31	38	49	1	17
Nausea	3	19	32	41	1	17
Chills	3	19	31	40	3	50
Headache	7	44	30	38	1	17
Fatigue	7	44	29	37	1	17
Hypophosphataemia	3	19	28	36	2	33
Hypokalaemia	2	13	26	33	1	17
Diarrhoea	6	38	25	32	3	50
Musculoskeletal pain	6	38	25	32	3	50
Hypoxia	6	38	24	31	2	33
Rash	4	25	24	31	0	0
Transaminases increased	3	19	24	31	2	33
Oedema	8	50	23	29	2	33
Tremor	4	25	23	29	1	17
Infection	5	31	22	28	3	50
Hypomagnesaemia	1	6	21	27	1	17
Constipation	2	13	19	24	1	17
Decreased appetite	4	25	17	22	0	0
Hypocalcaemia	1	6	17	22	2	33

Adverse Event[a]	0.5 x 10^6 cells/kg N=16		1.0 x 10^6 cells/kg N=78		2.0 x 10^6 cells/kg N=6	
	n	%	n	%	n	%
Leukopenia	4	25	17	22	0	0
Hyperglycaemia	5	31	16	21	1	17
Vomiting	2	13	16	21	1	17

Source: FDA Analysis; limited to terms with incidence of at least 20% in the 1.0 x 10^6 cells/kg target level
[a] Includes grouped terms

Table 51 shows the incidence of Grades 3-5 AEs by target KTE-X19 dose in decreasing frequency in the subgroup at the 1.0 x 10^6 cells/kg target level. Only AEs with an incidence of at least 5% are shown.

Table 51 FDA - Grades 3-5 TEAEs by Target KTE-X19 Dose in the Safety Population

Adverse Event[a]	0.5 x 10^6 cells/kg N=16		1.0 x 10^6 cells/kg N=78		2.0 x 10^6 cells/kg N=6	
	n	%	n	%	n	%
Anaemia	4	25	39	50	3	50
Neutropenia	5	31	38	49	1	17
Thrombocytopenia	6	38	35	45	2	33
Hypotension	5	31	30	38	3	50
Pyrexia	5	31	30	38	3	50
Hypophosphataemia	3	19	22	28	1	17
Encephalopathy	4	25	21	27	3	50
Cytokine release syndrome[b]	3	19	20	26	2	33
Hypoxia	3	19	18	23	1	17
Infection	5	31	17	22	1	17
Leukopenia	3	19	16	21	0	0
Transaminases increased	1	6	14	18	2	33
Febrile neutropenia	5	31	11	14	1	17
Hyperglycaemia	1	6	7	9	0	0
Respiratory failure	3	19	7	9	0	0
Bacterial infection	4	25	6	8	0	0
Hypocalcaemia	0	0	6	8	0	0
Diarrhoea	0	0	5	6	0	0
Lymphopenia	1	6	5	6	0	0
Tachycardia	0	0	5	6	1	17
Blood bilirubin increased	0	0	4	5	2	33
Coagulopathy	0	0	4	5	0	0
Delirium	0	0	4	5	1	17

Adverse Event[a]	0.5 x 10^6 cells/kg N=16		1.0 x 10^6 cells/kg N=78		2.0 x 10^6 cells/kg N=6	
	n	%	n	%	n	%
Fungal infection	0	0	4	5	0	0
Hypokalaemia	0	0	4	5	0	0
Musculoskeletal pain	0	0	4	5	1	17
Oedema	1	6	4	5	0	0
Seizure	0	0	4	5	0	0

Source: FDA Analysis; limited to terms with incidence of at least 5% in the 1.0 x 10^6 cells/kg target level
[a] Includes grouped terms
[b] Using CRS grading by Lee 2014

Clinical TL Review Comment: *There are trends for dose-toxicity relationships for all-grade Fever, CRS, Hypotension, Encephalopathy, Tachycardia, Chills, and Hypocalcemia; and for Grades 3-5 Hypotension, Fever, Encephalopathy, CRS, and aminotransferase elevation. This is consistent with the expected adverse reactions of KTE-X19.*

Impact of the Toxicity Management Strategy

As described in Section 8.2.1, the instructions for prevention and treatment of CRS and neurotoxicity were revised several times during the conduct of the protocol, and the instructions proposed for labeling are largely similar to those used for subjects treated after June 12, 2017. Table 47 shows the incidence of CRS and encephalopathy by dose in subjects treated before or after June 12, 2017 (note that no subjects with a target KTE-X19 dose of 2 x 10^6 cells/kg was treated after that date).

Table 52 FDA - CRS and Encephalopathy by Target KTE-X19 Dose and Change in Toxicity Management Strategy in the Safety Population

Adverse Reaction	Target KTE-X19 Cell Dose									
	0.5 x 10^6 cells/kg				1.0 x 10^6 cells/kg				2.0 x 10^6 cells/kg	
	Before[c] (N=4)		After[c] (N=12)		Before[c] (N=14)		After[c] (N=64)		Before[c] (N=6)	
	n	%	n	%	n	%	n	%	n	%
Any Grade CRS	3	75%	10	83%	14	100%	58	91%	6	100%
Grade 3-5 CRS[a]	2	50%	1	8%	4	29%	16	25%	2	33%
Any Grade Encephalopathy	2	50%	5	42%	12	86%	37	58%	5	83%
Grade 3-5 Encephalopathy[b]	2	50%	2	17%	8	57%	13	20%	3	50%

Source: FDA Analysis
[a] Lee 2014 grade for CRS
[b] CTCAE grade for encephalopathy
[c] Before or after June 12, 2017

Clinical TL Review Comment: *Within the cohort having a KTE-X19 target dose of 1.0 x 10^6 cells/kg (proposed dose for marketing) and with the most recent version of the toxicity*

management instructions (after June 12, 2017), there is a trend for a reduction in encephalopathy but not in CRS. Although these data should be interpreted with caution due to the small numbers of subjects, the results are clearly adequate to support the toxicity management instructions proposed.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Secondary malignancies are a potential risk associated with KTE-X19. As of the data cutoff date (09 September 2020), no secondary malignancies were causally attributed to KTE-X19 treatment.

The FDA's Assessment:

Secondary malignancy is a potential risk that may be associated with CAR T cell products. In the safety population, one subject had squamous cell carcinoma, and one subject had Carcinoma in situ which are not assessed to be related to KET-X19. Overall, no subject tested positive for RCR.

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies were reported in ZUMA-3.

The FDA's Assessment:

FDA Reviewer agrees.

Pediatrics and Assessment of Effects on Growth (If applicable)

The Applicant's Position:

Pediatric subjects were excluded from ZUMA-3.

The FDA's Assessment:

The ZUMA-3 study was limited to adult subjects 18 years of age and older. The Applicant submitted limited safety data for pediatric subjects enrolled in ZUMA-4 in the ISS datasets. No safety concerns were identified.

COVID-19 Related Safety Concerns

The Applicant tracked all site-level and subject-level protocol deviations related to COVID-19 that occurred during ZUMA-3. All COVID-19-related deviations were due to the impact of COVID-19 on scheduling and attending study visits. No subject in ZUMA-3 had a treatment-emergent COVID-19 infection.

Reviewer comment: *While the COVID-19 pandemic did affect some individual disease assessment time points, the overall study quality and results remain interpretable and were not considered impacted.*

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

KTE-X19 was first approved in the US on 24 July 2020 and in the EU on 14 December 2020. The reporting period for the first Periodic Benefit-Risk Evaluation Report was from 24 July 2020 to 23 January 2021; no postmarketing data were available at the time of writing of this document.

The FDA's Assessment:

An Empirica Signal Analysis for postmarketing safety issues was performed on FAERS data on 8/16/2021 (see Appendix 17.6). No new safety issues were identified.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

No significant safety issues for KTE-X19 emerged following the commercialization of this product, and the overall benefit-risk evaluation for KTE-X19 continues to be positive.

The FDA's Assessment:

REMS with ETASU will be implemented to ensure safe use in the postmarketing setting. Also, the Applicant will be required to conduct a PMR registry study to monitor for short- and long-term risks that may be related to KTE-X19.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The safety profile of KTE-X19 in subjects with B-ALL was manageable and the rates of identified risks were similar to those observed across different studies and treatment modalities and are consistent with the underlying disease. The overall rates of CRS and neurologic AEs in ZUMA-3 were generally comparable to those observed in ZUMA-2

{Wang 2020}, although a higher incidence of Grade 3 or higher CRS was observed in ZUMA-3. Risks associated with KTE-X19 have been well-characterized, and CRS and neurologic events observed in ZUMA-3 were generally reversible and treatable with medical intervention. Additional important identified risks associated with anti-KTE-X19 CAR T cell therapy (cytopenias, infections, and hypogammaglobulinemia) were also largely reversible and managed with antimicrobials and supportive care. The number of subjects who had worst Grade 3 or higher thrombocytopenia, neutropenia, or anemia that was present on or after Day 30 were 10 subjects (18%), 14 subjects (25%), and 4 subjects (7%), respectively. The risk of infection may be increased by neutropenia due to preparative lymphodepleting chemotherapy, pre-existing or treatment-induced hypogammaglobulinemia, prior cancer treatments, and underlying B-cell malignancy in subjects who receive KTE-X19 therapy. Subjects with an active infection, including localized infections, or inflammatory disease, should not be treated with KTE-X19 therapy until these conditions resolve. Hypogammaglobulinemia is an expected on-target toxicity of KTE-X19 due to B-cell depletion.

The results of the primary analysis of ZUMA-3 and safety profile from supportive studies demonstrate that KTE-X19 has a positive benefit-risk profile and is an important new therapeutic option for patients with r/r B-ALL.

The FDA's Assessment:

The Applicant submitted supportive safety data for four studies of KTE-X19 in subjects with r/r MCL (KTE C19-102 [ZUMA-2] n=82 subjects treated) and KT-US-472-0118 [ZUMA-18] Cohort 1 pooled, n = 103 subjects treated); pediatric r/r ALL (KTE-C19-104 [ZUMA-4] n = 36 subjects treated); and r/r chronic lymphocytic leukemia (CLL) (KTE-C19-108 [ZUMA 8], n = 9 subjects treated).

The ISS datasets were not updated by the Applicant to reflect FDA's adjudication of CRS, neurologic toxicity, and GTs etc. Furthermore, ZUMA-2 study was the primary study for the approved r/r MCL indication, and the data were reviewed in the original BLA submission. Therefore, for labeling purposes, the safety results for AESI (presented in Section 5 Warning and Precautions of the label) will not be based on the ISS datasets and thus will not be pooled but will rather be added and presented combined to reflect the incidence that would be included in the label.

Reviewer comment regarding labeling: *In Section 5 of the USPI, there were several AEs under the AESIs that were not grouped in the MCL indication per the GTs used in this application. For example, CRS related sinus tachycardia was not grouped under "tachycardia", aphasia and confusional state were not grouped under "encephalopathy", and agitation was not grouped under "delirium". Therefore, in order to correctly display these AEs incidences:*

- *Sinus tachycardia was added to tachycardia (for MCL)*
- *Aphasia and confusional state were ungrouped for ALL from GT "encephalopathy". Thus:*
    - *Aphasia occurred in 19 of 78 subjects (24%) with ALL. Incidence in subjects with MCL was 23%*
    - *Confusional state occurred in 22 of 78 subjects (28%) with ALL. Incidence in MCL was 24%*
- *Agitation was ungrouped for ALL from the GT "delirium". Thus*
    - *The incidence of agitation in ALL was 14% (11 subjects), while in MCL it was 11%.*

Among subjects with CRS across both MCL and ALL indications, key manifestations (>10%) included fever (93%), hypotension (62%), tachycardia (59%), chills (32%), hypoxia (31%), headache (21%), fatigue (20%), and nausea (13%). SAEs associated with CRS that occurred in ≥ 2% of subjects included: hypotension, fever, hypoxia, tachycardia, and dyspnea. The incidence of CRS (first occurrence) within the first seven days after KTE-X19 infusion was 83% (68/82) in subjects with MCL and 90% (70/78) in subjects with ALL. In all subjects combined (MCL/ALL), the incidence of first CRS within the first seven days after KTE-X19 infusion was 86% (138/160).

It is important to note that because the incidence of first CRS occurrence within the first seven days was not included in the currently approved USPI and was not included in the review memo of the MCL indication, the Reviewer ran the analysis of CRS within the first 7 days for MCL from the original submission 126703/0 ADAE dataset. This Reviewer identified 69 of 82 (84%) subjects while the Applicant identified 68 of 82 (83%) subjects. Since the difference was only 1% and thus was considered minor and because this Reviewer was not the Reviewer for the MCL indication, this Reviewer found the Applicant's incidence acceptable.

The most common neurologic events occurring in >10% of all subjects (MCL and ALL) combined included encephalopathy (57%), headache (36%), tremor (34%), confusional state (26%), aphasia (23%), , delirium (17%), dizziness (15%), anxiety (14%), and agitation (12%). SAEs occurring in ≥ 2% of subjects included encephalopathy, aphasia, confusional state, and seizures. The incidence of neurologic events (first occurrence) within the first seven days after KTE-X19 infusion was 56% (46/82) in subjects with MCL and 55% (43/78) in subjects with ALL. In all subjects combined (MCL/ALL) the incidence of neurologic events (first occurrence) within the first seven days after KTE-X19 infusion was 56% (89/160).

Among all 160 subjects with MCL and ALL, 91% experienced the first CRS or NT within the first seven days after KTE-X19 infusion. In all subjects combined NT resolved in 119 out of 134 (89%) subjects (52 of 66 (79%) subjects with MCL, and 67 of 68 (99%) subjects with ALL).

Infection of any grade occurred in 44% of subjects with ALL and in 56% of subjects with MCL and

thus in 50% of subjects combined. While Grade ≥ 3 infections occurred in 29%, 30%, and 30% in subjects with ALL, MCL, and all subjects combined, respectively. Infections included unspecified pathogen, bacterial, fungal, and viral infections.

Febrile neutropenia was observed in 6% of subjects with MCL and 35% of subjects with ALL. However, it is unclear if the review for MCL considered the overlapping individual events of fever and neutropenia into the incidence of febrile neutropenia.

Prolonged cytopenia will not be combined for the two indication because the cytopenia in subjects with ALL will be presented for the responders only.

Hypogammaglobulinemia occurred in 13% of subjects (16% in MCL and 9% in ALL).

Section 6 is not affected given that the ADR incidences are displayed separately for the MCL and ALL indications.

Reviewer comment: *Although the incidence of several AEs may differ numerically across studies, the safety data and key AEs are comparable. No additional safety concerns were noted from ZUMA-2, ZUMA-4, ZUMA-8, or ZUMA-18. There were no new safety signals identified and the safety profile of KTE-X19 remained unchanged.*

120-Day safety update

The 120-Day safety update to the sBLA was submitted on 29 July 2021 under eSeq 0122, which included events that occurred after the sBLA submission with data lock of 19 March 2021. The Applicant submitted narratives for new deaths that occurred in ZUMA-3 and the four other ZUMA supporting studies after the primary analysis data cutoff date of 09 September 2020.

Individual narratives of four subject (one from Phase 1 and 3 from Phase 2) who died in ZUMA-3 after the primary analysis data cutoff date were provided. See summary below:

- Subject ID (b) (6) : Phase 1. On Day 1429, subject died due to pulmonary graft versus host disease (GVHD).
- Subject ID (b) (6) : Phase 2. On Day 564, subject died due to progressive disease.
- Subject ID (b) (6) : Phase 2. On Day 560, the subject experienced an SAE of Grade 4 GVHD. On Day 773, subject died due to GVHD.
- Subject ID (b) (6) 4: Phase 2. On Day 554, the subject experienced an SAE of Grade 5 adenovirus infection.

Reviewer comment: *The safety profile of KTE-X19 remained consistent with what was observed in the original sBLA submission. No new safety concerns were identified.*

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

No statistical issues have been identified in this submission.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Efficacy

The primary evidence of effectiveness comes from Study ZUMA-3. This is a single-arm international, Phase 1/2 trial evaluating the safety and efficacy KTE-X19 in adult subjects with r/r pre-B ALL. Subjects were enrolled by undergoing leukapheresis. During manufacturing, subjects were to receive bridging therapy at the discretion of the investigator. All subjects were then treated with lymphodepleting chemotherapy followed by a single infusion of KTE-X19. As of the 9 September 2020 cutoff, 71 subjects were enrolled in the Phase 2 cohort, 55 were treated with KTE-X19 and 54 subjects met criteria to be included in the primary efficacy analysis. One subject was excluded because of lack of disease post-bridging chemotherapy. Manufacturing failure was observed in 8% of subjects.

The prespecified primary endpoint for the Phase 2 pivotal cohort, as defined by the Applicant, was OCR rate defined as the combined rate of CR + CRi as determined by central review. Using FDA-adjudicated results, the study met the bounds for the primary objective.

FDA has accepted CR with durability for determination of clinical benefit for regulatory decision-making. Additionally, since the clinical benefit is based on recovery of adequate blood counts to protect against infection and avoidance of transfusions, the precedent set response by 3 months from infusion as the timing for assessment of the endpoint.

The CR rate within 3 months of infusion of KTE-X19 was 52% (95% CI 38, 66). The duration of CR was estimated to exceed 12 months for more than half the subjects. A treatment effect was observed across the subpopulations. This is concluded to be substantial evidence of the effectiveness of KTE-X19 for treatment of adult subjects with r/r pre-B ALL.

The overall results of a high CR with durable response in a heavily pretreated population of adults with r/r ALL, even with a small sample size justifies a regular approval for KTE-K19. These results with a single agent indicate that the targeted KTE-X19 not only acutely treats the R/R ALL but has persistence that allows for a durable response.

The recommended KTE-X19 dosing is a target dose of 1 x 10^6 anti-CD19 CAR-positive viable T cells per kg body weight, with a maximum of 1 x 10^8 anti-CD19 CAR-positive viable T cells.

Safety

The safety analysis set included all 78 subjects who were treated with one dose of KTE-X19 at 1 x 10^6 cells/kg which is the intended dose for approval.

In summary:

- The most common non-laboratory adverse reactions (incidence ≥ 20%) included: fever, cytokine release syndrome (CRS), hypotension, encephalopathy, tachycardia, nausea, chills, headache, fatigue, febrile neutropenia, diarrhea, musculoskeletal pain, hypoxia, rash, edema, tremor, infection with pathogen unspecified, constipation, decreased appetite, and vomiting.
- The most comment Grade 3 or 4 laboratory abnormalities included: leukopenia (99%), neutropenia (97%), lymphopenia (96%), thrombocytopenia (87%), anemia (77%), hypophosphatemia (47%), increased alanine aminotransferase (31%), increased aspartate aminotransferase (23%), hyperglycemia (22%) and hypocalcemia (22%).
- Grade 3 or higher adverse reactions occurred in 76 (97%) subjects.
- SAEs occurred in 62 (79%) subject and included CRS, febrile neutropenia, hypotension, encephalopathy, fever, Infections with pathogen unspecified, hypoxia, tachycardia, bacterial infection, respiratory failure, seizure, diarrhea, dyspnea, fungal infection, viral infection, coagulopathy, delirium, fatigue, HLH/MAS, musculoskeletal pain, edema, and paraparesis.
- SAEs Grade 3 or higher occurred in 54 (37%) subjects and included hypotension, encephalopathy, fever, Infections with pathogen unspecified, hypoxia, tachycardia, bacterial infection, respiratory failure, seizure, diarrhea, dyspnea, fungal infection, viral infection, coagulopathy, delirium, fatigue, HLH, musculoskeletal pain, edema, and paraparesis.
- Four subjects had fatal adverse reactions: one with cerebral edema and three with infections (sepsis and fungal pneumonia). Three subjects with ALL had ongoing CRS events at the time of death.
- Most common Grade 3 or higher AESI included: prolonged cytopenias (47 subjects; 61%), febrile neutropenia (27 subjects; 35%), neurologic toxicities (27 subjects; 35%), infections (23 subjects; 30%), and CRS (20 subjects; 26%).
- Any grade CRS occurred in 72 (92%) subjects, and any grade neurologic toxicity occurred in 68 (87%) subjects.
- Among the 35 responders in the primary efficacy analysis set, four subjects (11%) had Grade 3 or higher prolonged cytopenia that didn't resolve by Day 60 and included neutropenia in 3 (9%) subjects and thrombocytopenia in two (6%) subjects.

Overall, except for HLH/MAS, no other new safety signals were identified in this submission.

CRS and neurologic toxicity associated with KTE-X19 therapy are serious, life-threatening and can be fatal. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. None of the secondary malignancies during this study was attributed to the study product but concern for insertional mutagenesis and secondary malignancies remain. Due to the lack of long-term safety data in the sBLA, a postmarketing long-term follow-up registry study will be required.

To enhance safety, the following measures should be followed:

- The product label includes a boxed warning for CRS and NT, and the warnings and precautions section conveys the treatment algorithm for CRS and NT management.
- HLH/MAS will be added to the warning and precaution section of the label
- Daily monitoring following KTE-X19 infusion will be revised in the label from 7 days to 14 days for patients with ALL.
- REMS with ETASU to assure the safe use of KTE-X19.
- PMR study that is a requirement to follow recipients of the commercial product for short term and long-term toxicity.

In summary, the Phase 2 portion of ZUMA-3 represents an adequate and well controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile in support of regular approval.

The review team recommends 1) granting regular approval for KTE-X19 for the treatment of adult patients with r/r pre-B ALL, and 2) not including MRD results in the USPI due to the assay validation concerns. The review team recommends approval for KTE-X19 under an ETASU REMS.

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented at an Advisory Committee meeting or to external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

10 Pediatrics

The Applicant's Position:

> KTE-X19 was granted Orphan Drug Designation on 20 April 2016 for the following indication: treatment of acute lymphoblastic leukemia. Per PREA and 21 CFR 314.55 and that this application is for an efficacy supplement, Kite claims exemption from the requirements of pediatric study requirements. Pediatric subjects were excluded from ZUMA-3.

The FDA's Assessment:

FDA agrees with the Applicant's position. KTE-X19 for treatment of ALL was granted Orphan Drug Designation (ODD). Per the Pediatric Research Equity Act (PREA) and 21 CFR 314.55(d), products with ODD are exempt from pediatric study requirements and therefore submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed. KTE-X19 original BLA for treatment of r/r MCL was submitted prior to August 18, 2020. Therefore, because this is a supplement BLA, Title V FDARA (which eliminates orphan exemption for pediatric studies for new molecular entities directed at relevant molecular targets) doesn't apply. The Applicant submitted statement of exemption from requirements for a pediatric assessment in m1.9.6.

ZUMA-3 study was limited to adult subjects 18 years of age and older. The Applicant submitted limited safety data for pediatric subjects enrolled in ZUMA-4 in the ISS datasets. However, the Applicant did not submit PK or exposure-response data to allow for extrapolation of efficacy to extend the age range in the indication.

11 Labeling Recommendations

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1.2 Indications and Usage, r/r B-ALL	TECARTUS is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).	TECARTUS is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
5.1 Warnings and Precautions, CRS	Include rates and severity of CRS observed following treatment with TECARTUS. (m5.3.5.3 ISS Ad hoc Dataset Table 14.3.2.6.4 and 14.3.4.3)	Include rate, severity and duration of CRS observed following treatment with TECARTUS based on FDA's adjudication.
5.2 Warning and Precautions, Neurologic Toxicities	Include rates and severity of neurologic toxicities observed following treatment with TECARTUS. (m5.3.5.3 ISS Ad hoc Dataset Table 14.3.4.4 and 14.3.2.8.6)	Include rate, severity and duration of neurologic toxicities observed following treatment with TECARTUS based on FDA's adjudication.
5.3 Warning and Precautions,	N/A	Add HLH/MAS to this section as an identified risk associated with KTE-X19 treatment
6.1 Clinical Trials Experience	Include ADRs and laboratory abnormalities observed in ZUMA-3 (m2.5, Table 8)	Include ADRs and laboratory abnormalities observed in ZUMA-3 based on FDA's adjudication of AEs, febrile neutropenia, and FDA's grouped terms. The safety population includes all subjects from Phase 2 and subjects from Phase 1 cohort who received KTE-X19 at the intended approved dose.
6.2 Immunogenicity	Include immunogenicity based on the ZUMA-3 Study (m2.7.4, Section 2.2.6.2 and CSR 11.2.8.2.2)	Include immunogenicity based on all treated subjects in the ZUMA-3 Study Phase 1/2
12.3 Pharmacokinetics	Include PK results following treatment with TECARTUS. (m2.5, Section 3.1; PK/PD Report, Section 2.2.1.	Include PK results following treatment with TECARTUS.
14.2 Clinical Studies, r/r B-ALL	Include efficacy data from ZUMA-3 Study (m2.5, Section 4.3, Table 5; m2.7.3; Section 3.3)	Include efficacy data from ZUMA-3 Study based on FDA's adjudication and FDA's efficacy population set. Also, include efficacy results for all leukapheresed subjects. Thus, key efficacy results will be displayed in one table:

		• The table will show response rates among the primary efficacy analysis population (n = 54) and among the all leukapheresed population (n = 71)] • The table will also include DOR within the primary efficacy analysis population for all responders Results will be displayed for the responders who achieved CR within the first 3 months from KTE-X19 infusion. MRD results cannot be included because of lack of MRD validation assays based on CDRH recommendation. In addition, survival data will not be included because of their limited value in a single arm study.

Abbreviations: ADR: adverse drug reaction; CRS: cytokine release syndrome; CSR: clinical study report; ISS: integrated summary of safety; PD: pharmacodynamics; PK: pharmacokinetics; r/r: relapsed/refractory

The Applicant's Position:

Based on the high complete remission rate, magnitude of improvements in durability of response and overall survival observed in ZUMA-3, and the manageable safety profile of TECARTUS (brexucabtagene autoleucel), the proposed therapeutic indication is for the treatment of patients with r/r B-ALL. Additional recommendations are summarized in the table above.

The FDA's Assessment:

Study ZUMA-3 represents an adequate and well controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile in support of regular approval. This is based on high CR rate and durable response coupled with acceptable safety profile in this heavily pretreated population. The recommended KTE-X19 dosing is a target dose of 1×10^6 anti-CD19 CAR-positive viable T cells per kg body weight, with a maximum of 1×10^8 anti-CD19 CAR-positive viable T cells. Notably, the approved dosing in MCL indication is 2×10^6 anti-CD19 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells.

Reviewer comment: *Labeling negotiations with the Applicant are ongoing at the time of completion of this review.*

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
Because of the risk of CRS and NT, KTE-X19 was originally approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). With the REMS, hospitals and their associated clinics that dispense KTE-X19 must be specially certified, and health care providers involved in the prescribing, dispensing or administering of KTE-X19 must be trained to recognize and manage CRS and nervous system toxicities.

At the presubmission meeting to discuss this sBLA, FDA agreed that a modification to the YESCARTA and TECARTUS REMS program will be necessary as part of the ZUMA-3 sBLA for r/r Pre-BLA. FDA agreed to the Applicant's plan to submit REMS major modifications related to ZUMA-3 within the first 30 days of the sBLA submission. The REMS submission included the REMS Document, REMS Supporting Document, REMS Educational Materials, and the Overview and Rationale including an impact assessment to the REMS with the potential addition of r/r FL and MZL to the label.

The Applicant submitted major REMS modification under 125703/108 and 125643/344.

Reviewer comment: *Negotiations between the OBE review team and the Applicant are ongoing at the time of this review. Refer to OBE review for details of the major REMS modification submissions. Overall, the Applicant agreed to FDA's edits and recommendation.*

In addition, the OBE review team recommended that the labeling changes regarding HLH/MAS and the daily monitoring of 14 days for patients with ALL be handled through a minor REMS modification. This is mainly because although HLH/MAS is a separate clinical entity from CRS or NT, the syndromes/symptoms often overlap. Hence, the OBE team will have sufficient time to review and to best incorporate the additional information into the REMS materials and knowledge assessment to ensure appropriate management of CRS and NT. Clinical team agreed to OBE's plan.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The pharmacovigilance plan (PVP) includes a long-term, prospective, non-interventional postmarketing requirement (PMR) registry study in subjects treated with KTE-X19.

As part of this sBLA, the Applicant planned to amend the long-term follow-up (LTFU) study for MCL, and proposed to enroll additional subjects with pre-B ALL.

The Applicant submitted a draft protocol KT-US-472-5655, entitled "Prospective Long-term Noninterventional Cohort Study of Recipients of TECARTUS for Treatment of Relapsed or Refractory Mantle Cell Lymphoma and Relapsed or Refractory Acute Lymphoblastic Leukemia" with the sBLA submission on 31 March 2021. The Applicant proposes to enroll 500 subjects with r/r ALL (in addition to the 500 subjects with MCL). The targeted accrual of 500 subject is based on the patient population and the projected proportion of patients likely to be treated with KTE-X19 in the postmarketing setting in the US over a 5-year enrollment period and consenting to participate in the study.

The proposed milestone dates for Protocol KT-US-472-5655 for r/r ALL indication were updated by the Applicant and submitted under eSeq 0125 on 05 August 2021. The milestones dates are as follow:

- Draft protocol submission: 31 March 2021*
- Final protocol submission: 15 October 2021
- Study complete date: 31 August 2041
- Final report submission: 31 August 2042

*The draft protocol was submitted with the initial sBLA submission (eSeq 0087)

Reviewer comment: *The OBE review team asked the Applicant to provide justification for their proposed sample size. The Applicant stated that considering that not all potential patients will receive KTE-X19 due to availability of other treatment options, limited access to approved treatment sites, prescriber preferences, and reimbursement status, the sample size of 500 subjects may be feasible. The Applicant also stated that Representatives from the Center for International Blood and Marrow Transplant Research (CIBMTR) suggest that, based on their previous CAR T cell therapy registry experience, they could enroll at least 60% of treated subjects into the registry. In addition, the proposed target sample size is also in alignment with the Applicant's experience with the registry study for KTE-X19 for the treatment of r/r MCL.*

The Applicant stated that the proposed sample size of 500 r/r pre- B-ALL patients in the US registry study will provide a 99%, 88%, 76%, 65%, or 57% chance of seeing at least 1 event of secondary malignancy, if the true rate per 15 years of follow up is at least 1:50, 1:100, 1:150,

1:200, or 1:250, respectively. This also assumes a piecewise survival curve with 55% survival at 2 years (based on a ZUMA-3 study estimate), 30% survival long-term, and 10% overall loss to follow-up.

The clinical and OBE review teams found the Applicant's justification for the proposed sample size to be acceptable.

Completion of Study KT-US-472-5655 is one of the postmarketing requirements for TECARTUS for r/r MCL under FDAAA Section 505(o)(3) and therefore, the Study Completion date and Final Report Submission date for r/r MCL have been agreed separately from the proposed dates for the r/r ALL indication.

14 Chief, Clinical Hematology Branch (CHB)

In reaching a recommendation for the regulatory basis for approval of TECARTUS for Adult ALL, the opinion of the Clinical Hematology Branch Chief differs from the review team. This reviewer recommends approval based on Overall Complete Response (OCR) in conjunction with CR and median duration of CR.

1) The clinical review team concluded that efficacy was based on CR with durability for determination of clinical benefit for regulatory decision making. In seeking clarity from the clinical review team as to whether overall complete response (OCR) which includes both CR and CRi, the CR and its durability was considered as the basis of primary efficacy, the clinical review team clarified that in the absence of statistical success following testing of the null hypothesis for OCR the study would have been considered have failed hypothesis testing and therefore would not have been considered for review of data to support CR.

2) OCR, per the review team would not be considered an appropriate endpoint for regulatory decision making as it includes CRi which is not considered an appropriate endpoint for regulatory decision making.

3) Thus, per the clinical review team, CR and the durability of CR were the sole basis for regulatory decision for traditional approval as OCR is not considered an endpoint to assess efficacy in ALL based-on regulatory precedence for approval of other products.

4) This reviewer clarified whether a pre-specified null hypothesis testing was proposed for CR endpoint as this is being considered as a regulatory efficacy endpoint. It was confirmed that there was no pre-specified testing for CR, but post-hoc, a hypothesis testing for null was set at threshold for null at "0" based on the assumption that if patients were not provided any treatment, CR would be 0%. The use of a no-treatment approach to evaluate a control rate is considered by the review team as reasonable, as available therapies were granted traditional approval obviating the need to demonstrate efficacy that is improved over standard of care.

5) This reviewer also discussed with the clinical review team, Oncology Center of Excellence (OCE) and Division of Hematological Malignancies – 1 (DHM-1), as to whether CRi could be considered a clinical benefit given the totality of the data, such that OCR could be considered as a clinical benefit endpoint. The clinical review team, noted that decisions to consider an endpoint of representative of clinical benefit could not be made after such data became available, the consideration of CRi as a clinical benefit endpoint

in ALL impacts the regulatory review and advice given to investigational products in clinical development program for ALL. Further clarifications were also obtained with the clinical review team, OCE and DHM-1 as to the level of evidence required to determine an endpoint as reasonable for efficacy as part of the clinical development program, and the conclusion was a decision to consider an endpoint to be of clinical benefit or reasonably likely to predict for clinical benefit required pooling of data and meta-analysis. However, in the instance of ALL it was also confirmed that the use of CR wasn't specifically determined on the basis of pooled data or such meta-analysis and prior approvals were based, as noted in the Assessment Aid based on CR and regulatory precedence was thus set.

6) Based on the internal discussions with OCE and DHM-1, the need for null hypothesis testing of the efficacy endpoint used for regulatory decision making was clarified in that for a single arm study, a pre-specified null hypothesis testing was not required but a decision to grant approval could be based on the risk-benefit determination based on the endpoint under consideration for regulatory decision making.

This reviewer has taken these discussions into consideration and the basis for regulatory recommendation continues to differ from the review team and input from OCE and DHM-1. For these reasons, this reviewer documents here, the considerations and basis for use of OCR as the primary endpoint upon which this reviewer makes a regulatory recommendation.

1) In the absence of a pre-specified null hypothesis testing of the efficacy endpoint (CR) for regulatory decision making the study would not meet the standards for an adequately designed study to meet the regulatory considerations for an adequate and well-controlled study.

2) Introduction of a post-hoc null hypothesis testing for CR would not be considered as meeting the standards of regulatory review and introduces bias.

3) Introduction of no-treatment effect null threshold of 0 for CR, is yet to be supported by evidence.

4) If such a null threshold is applicable to CR post-hoc, consideration for a post-hoc introduction of null hypothesis testing based on a threshold of 0 could be considered for CRi.

5) The absence of a requirement for pooling of data and meta-analysis in determining a CR as a clinical benefit endpoint based on regulatory precedence also introduces

consideration of CRi as a clinical benefit endpoint based on the totality of data (as noted below).

6) In examining whether OCR is reasonable consideration as an efficacy endpoint particularly inclusion of CRi as within OCR for regulatory decision making, the following aspects of the data were considered.

    a. The data from the study in Tables 13 and 15 of the Assessment Aid, evaluating the clinical benefit of CRi and the durability as evidenced in a sample size of 6 subjects of an estimated median duration of response of 6.9 mo and 95% CI: 1.0, NE, median follow up time 3 months, (Range: 0.03-10.2 months) with 50% of patients being censored (1 patient following receipt of allo-SCT, and other who progressed at D432 but censored at an earlier timepoint for missing data, and one subject with ongoing remission at data cut off.

    b. This reviewer agrees that the DOR for subjects achieving CRi with TECARTUS may be lower than that observed with CR (please refer to Table 15). Therefore, regulatory precedence was reviewed to understand the magnitude of benefit that was the basis for considerations in granting prior therapies. It should be noted that per the package insert for blinatumomab, the approval in pediatric ALL an initial approval for this product, (which is considered for FDA review purposes as not biologically different from adult ALL), was based on 12% CR (95% CI: 9.2,28) and median DOR of 6 mo (range: 0.5-12.1). In combination with CR/CRh the CR rate was 23% (95% CI: 22-45) and median DOR of 6 mo (range: 0.5-16.4). The CR rate and duration of CR, in addition to the proportion of patients with MRD negative CR/CRh were the basis for consideration of efficacy. This reviewer notes that the efficacy was not considered based on the CRh rate. Thus, this reviewer concludes that the magnitude of benefit observed for CRi for TECARTUS in the ZUMA 3 study is similar in both the magnitude of CR and the median DOR for patients in CR observed in the study that was used to determine efficacy of blinatumomab.

    c. In reviewing the literature to determine the benefits of CRi or lack of benefits of CRi and its relation to DOR, the reviewer was unable to find a reasonable body of evidence regarding this issue or the reduction in benefit due to the need for transfusion support. Although it is not clear from the review whether subjects who experienced durable responses observed in two of the subjects with delayed disease progression or were censored required transfusion support

through the entirety of their response and the frequency with which it was required, achieving remission sufficient to avoid additional chemo or immunotherapy for reasonable time period as observed in the ZUMA 3 study or alternatively have disease control to permit allo-stem cell transplantation (SCT) is representative of benefit even when the need for transfusion is considered. Note is also made that for CIBMTR registry data collection purposes representative of real-world management of patients, the definition of CRi is less stringently applied than with the clinical studies under regulatory review in that transfusions that are related to the effects of chemotherapy can be counted towards CR instead of CRi. Given the known adverse event of prolonged cytopenia as noted in the existing package insert for Tecartus, the presence of prolonged cytopenia requiring transfusion support may be related to the product in itself rather than solely due to prognostic reasons.

d. While regulatory precedence of utilizing an endpoint is important to maintain review consistency, additional considerations based on the totality of data, the substantial CR rates observed with this class of products as compared to other approved products, the durability observed with this class of products warrant regulatory flexibility in assessing the data that are indicative of clinical benefit. This reviewer considers that CRi in addition to CR as representing a clinical benefit and therefore warrants consideration of OCR as the primary endpoint.

For these reasons, this reviewer recommends that the primary basis for efficacy is based on OCR (and consistent with the statistical review memo) in conjunction with CR and its durability. This reviewer also recommends that labelling verbiage also be revised to include that OCR in addition to CR and its DOR were considered in the regulatory decision making for efficacy as the current verbiage alludes to CR and its durability as the basis for efficacy.

15 Oncology Center of Excellence (OCE) Signatory

I agree with the recommendations from Drs. Bouchkouj, Przepiorka, and George for regular approval of brexucabtagene autoleucel for the treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (pre-B ALL). I also agree with the conclusions of the primary review team that:

"Study ZUMA-3 represents an adequate and well-controlled study that provides substantial evidence of effectiveness based on complete response rate and durability of response in subjects with r/r pre-B ALL in the context of an acceptable safety profile in support of regular approval. Given the life-threatening nature of the disease in the indicated population, the adverse reactions of CRS and NT, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective in the intended population. Thus, the overall benefit-risk profile favors regular approval of KTE-X19 in adult patients with r/r pre-B ALL."

While the trial met its prespecified primary endpoint with an OCR (CR + CRi) rate of 65% (95% CI: 51, 77), durable CR has served as a primary basis for regular approval. CR as an endpoint provides a high level of certainty that this reduction in tumor burden is attributable to the treatment rather than natural history, is well-defined and reliably assessed, and as discussed in FDA guidances has been associated with decreases in transfusion requirements, decrease in infections, and decrease in bleeding. While CRi has been used as a measure of anti-tumor activity, CRi as an endpoint is not currently recommended for use in the primary determination of the efficacy in registration trials of products for acute leukemia indications. Additional information is needed to support that treatment effects on CRi are representative of clinical benefit.

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

16 Division Director (DCEPT)

I agree with the clinical review team, CHB Branch Chief, and OCE that the Applicant has provided substantial evidence of effectiveness and safety from an adequate and well controlled clinical trial, ZUMA-3, to support the regular approval of brexucabtagene autoleucel for the treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (pre-B ALL).

I appreciate the discussion regarding the endpoints that formed the primary basis of approval, to include regulatory precedence for approval of therapies for ALL based on CR and DOR, which were demonstrated by the Applicant in this efficacy supplement, and Dr. George's regulatory considerations for OCR as the primary basis for approval in conjunction with CR and DOR.

As the Applicant met the prespecified primary efficacy endpoint with an OCR of 65% (95% CI: 51, 77) and demonstrated clinically meaningful benefit in CR and DOR, I consider OCR in combination with CR and DOR as providing the primary basis for regular approval of brexucabtagene autoleucel for the treatment of r/r pre-B ALL.

17 Appendices

17.1. References

The Applicant's References:

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FDA's References:

Please refer to the footnotes throughout the document for FDA's references and citations.

17.2. Financial Disclosure

The Applicant's Position:

Financial disclosure forms were completed by investigators participating in ZUMA-3, in conformance with 21 CFR 54. The applicant identified 14 investigators who received significant payments of other sorts (SPOOS) ≥ $25,000. One additional investigator self-disclosed financial interests and are included for transparency, however Kite records indicate SPOOS < $25,000. Thirteen investigators did not sign financial disclosure forms, and certification of due diligence has been provided. Additional details are in m1.3.4 Financial Certification and Disclosure.

Kite has taken steps to minimize the potential bias of clinical study results by developing data handling procedures that maintain trial credibility and validity. The primary analysis of efficacy was based on an independent review committee assessment, independent from investigator assessment of response. The evaluation of safety results, including AEs and laboratory results, were verified in source documents by the site monitor. Through these measures, the financial interests of the investigators have minimal potential for introducing bias into the study results.

The FDA's Assessment:
The Applicant employed appropriate risk-reduction strategies to minimize bias and adequately 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-3's conduct or findings. See Table 53 for details.

Table 53 ZUMA-3: Covered Clinical Study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 550		
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): 14		
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: 14 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 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) 13		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above was filled by the Applicant and confirmed by the FDA

17.3. Schedule of Assessments

Table 54 ZUMA-3: Schedule of Assessments: Screening, Pretreatment, Treatment, Posttreatment Follow-up

Visit Frequency / Procedures	Screening[a]	Enrollment/ Leukapheresis	Bridging Chemotherapy	CSF Prophylaxis	Lymphodepleting Chemotherapy Period				IP Administration Period[b]		Post-treatment Follow-up[b,c] (each visit calculated from Day 0)			
	≤ 14 days before enrollment	≤ ~5 days after eligibility confirmation			Day −4	Day −3	Day −2	Day −1	Day 0	Day 1 to Day 7[d]	Day 14 (± 2 days)	Day 28 (+ 3 days)	Week 8 (± 1 week)	Month 3 (± 2 weeks)
Medical history	X													
Physical examination	X										X	X	X	X
Vital signs[e]	X[e]	X[f]	X[g]	X[g]	X	X	X		X[e]	X[e]	X	X	X	X
Weight	X	X[f]												
ECOG performance status	X				X				X					
Neurological assessment[h]	X								X	X[h]		X		X
EQ-5D (Phase 2 subjects only)[i]	X								X			X		X
ECG	X[a]													
LVEF and PE assessment by ECHO	X[a]													
Chest x-ray	X													
Bone marrow evaluation (biopsy and aspirate) for disease assessment[j]	X				X					Opt. Day 7 Bx & A		X	X	X
Extramedullary imaging[k]	X											X	X	X
Overall response assessment												X	X	X
Leukapheresis[f]		X												
CSF prophylaxis[l]	X													
Bridging chemotherapy[l]		X												
Lymphodepleting chemotherapy (fludarabine/cyclophosphamide)[l]					X	X	X							
KTE-X19 infusion IV									X[m]					
Pregnancy test (serum or urine β-HCG)	X				X									X

Procedures / Visit Frequency	Screening[a] ≤ 14 days before enrollment	Enrollment/ Leukapheresis ≤ ~5 days after eligibility confirmation	Bridging Chemotherapy	CSF Prophylaxis	Lymphodepleting Chemotherapy Period: Day −4	Day −3	Day −2	Day −1	IP Administration Period[b]: Day 0	Day 1 to Day 7[d]	Post-treatment Follow-up[b,c] (each visit calculated from Day 0): Day 14 (± 2 days)	Day 28 (+ 3 days)	Week 8 (± 1 week)	Month 3 (± 2 weeks)
Chemistry panel and CBC with differential[g]	X	X[f]	X[g]	X[g]	X	X	X		X	X	X	X	X	X
CD3 count		X[f]												
CD19 immunophenotyping	X[a]													
C-reactive protein		X[f]												
Lumbar puncture for collection of CSF[a]	X			X					X			X		
Anti-KTE-X19 antibody		X[f]										X		X
Peripheral blood	X[g]			X[g]										
Blood draw for PBMCs[b]		X[f]			X[i]					Day 7	X	X	X	X
Blood draw for cytokines[b]		X[f]			X[i]				X	Day 3 and 7	X	X		
AEs/concomitant medications	X	→												

Abbreviations: AE, adverse event; β-HCG, beta-human chorionic gonadotropin; Bx & A, biopsy and aspirate; CBC, complete blood count; CNS, central nervous system; CR, complete remission; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life-5 Dimensions; EU, European Union; HIV, human immunodeficiency virus; IHC, immunohistochemistry; IP, investigational product; IV, intravenous; LVEF, left ventricular ejection fraction; MRD, minimal residual disease; Opt., optional; PBMC, peripheral blood mononuclear cell; PE, pulmonary embolism; RCR, replication-competent retrovirus; SCT, stem cell transplant; SOA, schedule of assessments.

a Screening procedures: Procedures were to be performed within 14 days of enrollment (unless otherwise specified). ECG: ECG was to be performed within 30 days prior to enrollment. ECHO: If the last chemotherapy regimen the subject received was not considered cardiotoxic, then an ECHO performed within 28 days prior to signing the consent could be used for eligibility. If the last chemotherapy regimen the subject received was considered cardiotoxic, then an ECHO performed following the subject's last chemotherapy treatment and within 28 days prior to signing the consent could be used for confirmation of eligibility. CD19: Local CD19 immunophenotyping was to be performed at screening on peripheral blood or bone marrow aspirate. Surface CD19 expression was to be measured by flow cytometry; IHC analysis was allowed if the bone marrow aspirate was a dry tap or inadequate or if there were insufficient circulating blasts for flow cytometry. Procedures that were part of standard of care were not considered study-specific procedures and could be performed prior to obtaining consent and used to confirm eligibility provided they were performed within the time allowance as outlined in the SOA.

b Following the initial hospitalization for the KTE-X19 infusion, if the subject was hospitalized with any KTE-X19-related AE, a blood sample for PBMCs and cytokines was to be collected on the day of admission, then weekly, and on the day of discharge. A PBMC sample was to be collected at the time of progression and prior to starting subsequent anticancer therapy. As applicable, an additional cytokine sample was to be drawn at the first onset and first reoccurrence of any Grade 2 or higher CRS (per {Lee 2014} criteria) if not already collected on that day. In addition, blood draws for PBMCs were to be used for the analysis of RCR at baseline, Month 3, Month 6, and Month 12. Thereafter, samples were to be collected yearly and held for up to 15 years. If a subject tested positive for RCR at any time point within the first year, samples were to be collected and tested yearly for up to 15 years or as clinically indicated.

c If the subject progressed before Month 3: Refer to Appendix 16.1.1.1, Protocol Amendment 6, Section 7.11.8 for the procedures that were to be completed.
d Refer to Appendix 16.1.1.1, Protocol Amendment 6, Appendix 3 for requirements by country regulatory agencies.
e Vital signs: Included blood pressure, heart rate, oxygen saturation, and temperature. Height was to be collected at screening. Vitals were to be monitored before and after the KTE-X19 infusion and then routinely (every 4 to 6 hours) while hospitalized. If the subject had a fever (temperature ≥ 38.3°C) at any time during hospitalization, vital signs were to be monitored more frequently as clinically indicated.
f Leukapheresis: All leukapheresis criteria were to be met before leukapheresis commenced. Vital signs, weight, and laboratory sample draws could be performed on the day of or before leukapheresis, except weight was to be collected on the day of leukapheresis. All laboratory samples were to be drawn before the leukapheresis procedure. For EU sites, viral serologic tests (eg, HIV, hepatitis B, and hepatitis C) were to be carried out per institutional guidelines and EU regulations. This could be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.
g Vital signs, chemistry panel, and CBC: Collected each day prior to CSF prophylaxis and bridging chemotherapy. CBC 5-part was preferred, but 3-part was acceptable. Peripheral blood: Peripheral blood was to be collected at screening, and if the subject did not have bridging therapy, then peripheral blood was to be collected during Day −4 and submitted to the central laboratory.
h Neurological assessment: Subjects' neurological status were to be evaluated at screening to establish a baseline. After enrollment, subjects were to be evaluated for any neurological symptoms at each of the time points specified in the SOA. During the hospitalization period, evaluations of neurological status may have needed to be increased.
i EQ-5D: The EQ-5D was to be completed prior to other study-related procedures or assessments.
j Bone marrow evaluation (biopsy and aspirate) for disease assessment: For screening bone marrow evaluation, see Appendix 16.1.1.1, Protocol Amendment 6, Section 7.9.1. A bone marrow aspirate was required at all time points indicated. (For subjects who received an SCT, bone marrow evaluations were not required for the first 100 days after SCT). In addition to the bone marrow aspirate, a bone marrow biopsy was required at screening, Day −4, and Day 28. The Day −4 bone marrow biopsy was only required for subjects receiving bridging chemotherapy. A bone marrow biopsy at all other time points was recommended and was to be performed if standard of care. Any time the bone marrow aspirate was a dry tap, then a bone marrow biopsy was required. Disease status was to be evaluated per institutional practices. A portion of the aspirate collected was to be submitted to the central laboratory on the day of collection and analyzed for MRD. The optional Day 7 bone marrow biopsy and aspirate could be performed between Day 7 and 14. Overall response was to be assessed by the investigator per Table 5. If bone marrow blasts were ≤ 5% and circulating blasts were ≥ 1%, then additional studies (eg, flow cytometry) were to be performed to quantify the blasts.
k Extramedullary imaging: For subjects with known baseline extramedullary disease detected through imaging, baseline images appropriate for the anatomical location and clinical scenario were to be performed. For subjects receiving bridging chemotherapy, images were to be performed after bridging chemotherapy and before lymphodepleting chemotherapy. For subjects not receiving bridging chemotherapy, images were to be performed within 28 days before lymphodepleting chemotherapy. On-study images were to be performed with the same imaging modality and anatomical location as imaged at baseline. Following KTE-X19 infusion, the first on-study images were to occur at the first occurrence of leukemia remission based on the bone marrow evaluation. Subsequent images were to continue per the SOA through Month 24 or disease progression, whichever occurred first. If the subject's disease had not progressed by Month 24, then images were to be performed per standard of care until disease progression. For subjects with or without extramedullary disease, images were to be performed per standard of care any time the subject presented with symptoms suggestive of disease progression.
l Chemotherapies: Bridging chemotherapy was to be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever was shorter, prior to initiating lymphodepleting chemotherapy. CSF prophylaxis was to be administered any time during screening through 7 days before the KTE-X19 infusion. Subjects who were enrolled with CNS-2 disease at baseline were to receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19 infusion, unless otherwise approved by the Kite medical monitor. Multiple doses of CSF prophylaxis could be given per investigator discretion in accordance with institutional guidelines, but at least 7 days were to pass between the last dose of CSF prophylaxis and KTE-X19 infusion. Should a subject have an Ommaya reservoir with no evidence of blockage of CSF flow from the spinal canal, administration of CSF prophylaxis through the reservoir was acceptable. Lymphodepleting chemotherapy, consisting of fludarabine on Days −4, −3, and −2 prior to KTE-X19 infusion and cyclophosphamide on Day −2 prior to KTE-X19 infusion, was to be administered.
m KTE-X19 premedications: Subjects were to receive acetaminophen and diphenhydramine (equivalent) approximately 1 hour prior to KTE-X19.
n Lumbar puncture: CSF samples were to be analyzed locally for disease assessment and centrally for disease assessment and toxicity evaluation at the following time points: 1) baseline (a CSF result obtained within 30 days before enrollment was considered acceptable eligibility determination); 2) at the time of CSF prophylaxis; 3) for subjects with baseline CNS-2 disease, a CSF sample was required at the time of first presumed response based on bone marrow (bone marrow < 5%); 4) first onset of Grade 2 or higher neurological symptoms or as medically indicated; 5) for subjects with a CR, collection and analysis of CSF was required to confirm CR; and 6) per institutional standard of care. Should a subject have an Ommaya reservoir with no evidence of blockage of CSF flow from the spinal canal, withdrawal of the CSF sample though the reservoir was acceptable. CSF samples (ie, those collected on or after informed consent) were to be submitted to the central laboratory.

Source: CSR Page 47

Table 55 ZUMA-3: Schedule of Assessments: Long-term Follow-up

Procedures \ Visit Frequency	Long-term Follow-up Period[a] (Each visit calculated from Day 0)												
	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 Up to 15 Years
Physical examination	X	X	X	X	X	X							
EQ-5D (Phase 2 subjects only)	X	X	X	X	X	X							
Bone marrow evaluation (biopsy and aspirate) for disease assessment[b]	X	X	X	X	X	X							
Extramedullary imaging[c]	X	X	X	X	X	X							
Overall response assessment	X	X	X	X	X	X							
Survival status[a,d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential (5-part preferred, 3-part acceptable)	X	X	X	X	X	X							
Anti-KTE-X19 antibody[a,f]													
Blood draw for PBMCs[a]	X	X	X	X	X	X		X		X		X	X
AE/SAE reporting[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications reporting[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for ALL[a,h]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ALL, acute lymphoblastic leukemia; CBC, complete blood count; CRF, case report form; EQ-5D, European Quality of Life-5 Dimensions; GVHD, graft-versus-host disease; ICF, informed consent form; PBMC, peripheral blood mononuclear cell; RCR, replication-competent retrovirus; SAE, serious adverse event; SCT, stem cell transplant; SOA, schedule of assessments.

a Blood draws for PBMCs were to be used for the analysis of RCR at baseline, Month 3, Month 6, and Month 12. Thereafter, samples were to be collected yearly and held for up to 15 years. If a subject tested positive for RCR at any time point within the first year, samples were to be collected and tested yearly for up to 15 years or as clinically indicated. If the subject progressed in the long-term follow-up phase, the subject was to be followed for survival status and subsequent therapy for ALL and have blood drawn for PBMCs and, if applicable, anti-KTE-X19 antibodies. A PBMC sample was to be collected at the time of progression and prior to starting subsequent anticancer therapy.

b Bone marrow evaluation (biopsy and aspirate) for disease assessment: A bone marrow biopsy and aspirate were to be performed per the SOA through Month 24 or until disease progression, whichever occurred first. Disease status was to be evaluated per institutional practices. The slides used for the local evaluation of % blasts were to be submitted to the central laboratory along with the corresponding pathology report. If the subject's disease had not progressed by Month 24, then bone marrow evaluation was to be performed per standard of care.

c Extramedullary imaging: For subjects with baseline extramedullary disease: Following KTE-X19 infusion, the first on-study images were to occur at the first occurrence of leukemia remission based on the bone marrow evaluation. Subsequent images were to continue per the SOA through Month 24 or disease progression, whichever occurred first. If the subject's disease had not progressed by Month 24, then images were to be performed per standard of care until disease progression. For subjects with or without extramedullary disease, images were to be performed per standard of care any time the subject presented with symptoms suggestive of disease progression.

d AE/SAE reporting: AEs: After 3 months, only targeted AEs were to be reported in the CRF through 24 months after KTE-X19 infusion or disease progression, whichever occurred first. SAEs: After 3 months, only targeted SAEs (including targeted Grade 5 SAEs) were to be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurred first, within 24 hours using the SAE Report Form and on the CRF. Targeted AEs included central neurological, hematological, infections, GVHD, autoimmune disorders, and new/secondary malignancies. Subjects who received an allogeneic SCT were only to be followed for KTE-X19-related SAEs. Reporting of these SAEs was to commence at the time the SCT preparative regimen commenced through 24 months after KTE-X19 infusion or disease progression, whichever occurred first, within 24 hours using the SAE Report Form and on the CRF. In addition to the above SAE reporting requirements, any time a KTE-X19-related SAE occurred, it was to be reported within 24 hours using the SAE Report Form and on the CRF. All deaths that occurred from signing of the ICF through end of study were to be reported in the CRF.

e Survival status: Subjects could be contacted by telephone to confirm survival status.

f Anti-KTE-X19 antibodies: For antibody sample collection in long-term follow-up, refer to Appendix 16.1.1.1, Protocol Amendment 6, Section 7.11.9.

g Concomitant medications reporting: After 3 months of follow-up, only targeted concomitant medications were to be collected for 24 months after KTE-X19 infusion or disease progression, whichever occurred first. Targeted concomitant medications included gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

h Subsequent therapy for ALL: Documentation of subsequent therapy for ALL was to continue to be documented while the subject remained on-study. Subjects could be contacted by telephone.

Source: CSR Page 50

17.4. Disease Response

Table 56 ZUMA-3: Overall Disease Response Classification

Response	BM[a]		Peripheral Blood[b]		CNS EMD		Non-CNS EMD[c]
CR	≤ 5%	*and*	ANC ≥ 1,000 and Plt ≥ 100,000	*and*	CNS-1	*and*	CR[d]
CRi			ANC ≥ 1,000 and Plt < 100,000 OR ANC < 1,000 and Plt ≥ 100,000				
CRh			ANC ≥ 500 and Plt ≥ 50,000 but not CR				
BFBM			Any values not meeting criteria for CR, CRi, or CRh				
PR	All criteria for CR, CRi, CRh, or BFBM were met					*and*	PR
Relapse	> 5%	*or*	Circulating leukemia present[e]	*or*	CNS-2 or CNS-3	*or*	PD
No response	All required assessments were performed with failure to attain the criteria needed for any response category						
Unknown	Assessment was not done, incomplete, or indeterminate Note: Overall disease response could be assessed as 'relapsed disease' if any single element of disease response assessment showed relapse; other unknown elements of disease response assessment did not need to be evaluated						

Abbreviations: ANC, absolute neutrophil count; BFBM, blast-free hypoplastic or aplastic bone marrow; BM, bone marrow; CNS, central nervous system; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; EMD, extramedullary disease; Plt, platelets; PR, partial remission.

a Blasts by morphology in BM.

b The units for ANC and Plt are per μL. ANC and Plt values were to be evaluated every time a BM evaluation was performed. If not done, ANC and Plt values used for response assessment could be from any time 7 days before the BM result to any time after the BM result.

c Refer to the EMD disease response table in Appendix 16.1.1.1, Protocol Amendment 6, Appendix 2. In subjects evaluated for non-CNS EMD, imaging and BM results used for assessment of overall disease response were to be within 30 days of each other.

d If baseline EMD was present, then images must have shown CR. If no baseline EMD was present, then images were not required, but if performed, images must have shown CR per Appendix 16.1.1.1, Protocol Amendment 6, Appendix 2.

e No circulating leukemia was defined as < 1% circulating blasts by morphology; circulating leukemia was defined as ≥ 1% circulating blasts by morphology. If ≥ 1% blasts by morphology and there was no other evidence of leukemia, then flow or molecular studies were to be conducted to confirm that blasts were leukemia.

Source: CSR Page 53

Table 57 ZUMA-3: Extramedullary Disease Response Classification

Response [a]	PET Baseline, On-study		Baseline lesion(s) (by CT or MRI) [b]		New Lesion(s)

CR	Neg, N/A	*and*	All of:
			• Disappearance of measurable and non-measurable nodal lesions:
			  ○ Nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD
			  ○ Nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0cm in their short axis after treatment
			• If testes, spleen and/or liver involvement, they must be normal size by imaging or physical examination.
				and	No

	Pos, Neg	*and*	Any	*and*	No
PR	Any	*and*	All of: • ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant masses. Dominant masses should be clearly measurable in at least 2 perpendicular dimensions, and should be from different regions of the body if possible. • No increase in size of liver or spleen by imaging or physical exam • If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for a single nodule.	*and*	No
SD	Does not meet the criteria for CR, PR, or PD				
PD	Any	*and*	At least one of the following: • ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node. • At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis • Greater than or equal to a 50% increase in size of splenic, hepatic or any other non-nodal lesion.	*or*	Yes

Neg = Negative; Pos = Positive; N/A = Not applicable
a Modified Revised IWG Criteria (Cheson et al, 2007)
b see Section 7.9.2 of protocol for details.

Source: ZUMA-3 Protocol Amendment # 6 Page 99

17.5. FDA Grouped Terms

Grouped terms that were used for FDA analyses of adverse events are listed in Table 58 below.

Table 58 FDA Grouped Terms Used for FDA Analyses of Adverse Events

FDAGT*	AEDECOD**
Abdominal pain	Abdominal discomfort
	Abdominal pain
	Abdominal pain upper
Acute lymphocytic leukaemia	Acute lymphocytic leukaemia
	B-cell type acute leukaemia
Amenotransferase increased	Alanine aminotransferase
	Alanine aminotransferase increased
	Aspartate aminotransferase increased
	Transaminases increased
Arrhythmia	Arrhythmia
	Arrhythmia supraventricular
	Atrial fibrillation
	Atrial flutter
	Atrial tachycardia
	Bradycardia
	Cardiac arrest
	Electrocardiogram QT prolonged
	Electrocardiogram T wave inversion
	Pulseless electrical activity
	Sinus bradycardia
	Supraventricular tachycardia
	Ventricular tachycardia
Ataxia	Ataxia
	Dysmetria
	Gait disturbance
Bacterial infection	Anorectal cellulitis
	Bacteraemia
	Bacterial disease carrier
	Cellulitis
	Cellulitis of male external genital organ
	Cellulitis staphylococcal
	Clostridial infection
	Clostridium difficile colitis
	Clostridium difficile infection

FDAGT*	AEDECOD**
	Enterococcal bacteraemia
	Enterococcal infection
	Escherichia bacteraemia
	Escherichia infection
	Escherichia sepsis
	Pseudomonas infection
	Staphylococcal bacteraemia
	Staphylococcal infection
	Vulval cellulitis
	Wound infection staphylococcal
Cardiac failure	Cardiac failure
	Ejection fraction decreased
Coagulopathy	Blood fibrinogen decreased
	Coagulopathy
	Disseminated intravascular coagulation
	Hypofibrinogenemia
	International normalised ratio increased
Cough	Cough
	Productive cough
	Upper-airway cough syndrome
Delirium	Agitation
	Delirium
	Delusion
	disorientation
	Hallucination
Diarrhoea	Colitis
	Diarrhoea
	Diarrhoea haemorrhagic
Dizziness	Dizziness
	Presyncope
	Syncope
	Vertigo
Encephalopathy	Altered state of consciousness
	Amnesia
	Aphasia
	Cognitive disorder
	Confusional state
	Depressed level of consciousness
	Disturbance in attention

FDAGT*	AEDECOD**
	Dysarthria
	Dysgraphia
	Encephalopathy
	Lethargy
	Memory impairment
	Mental status changes
	Slow speech
	Slow response to stimuli
	Somnolence
	Speech disorder
	Toxic encephalopathy
Fatigue	Asthenia
	Cancer fatigue
	Fatigue
	Malaise
Fever	Pyrexia
Fungal infection	Bronchopulmonary aspergillosis
	Candida infection
	Fungal skin infection
	Mycotic endophthalmitis
	Oral candidiasis
	Osteomyelitis fungal
	Pneumocystis jirovecii pneumonia
	Pneumonia fungal
	Sinusitis fungal
	Systemic candida
Graft versus host disease	Graft versus host disease
Haematoma	Subdural haematoma
	Tongue haematoma
Haemorrhage	Abdominal wall haemorrhage
	Catheter site haemorrhage
	Conjunctival haemorrhage
	Contusion
	Epistaxis
	Gastric haemorrhage
	Gastrointestinal haemorrhage
	Gingival bleeding
	Haematochezia
	Haematoma

FDAGT*	AEDECOD**
	Haematoma muscle
	Haematuria
	Haemoptysis
	Haemorrhage
	Haemorrhage intracranial
	Haemorrhoidal haemorrhage
	Large intestinal haemorrhage
	Lower gastrointestinal haemorrhage
	Melaena
	Menorrhagia
	Petechiae
	Pharyngeal haemorrhage
	Post procedural haemorrhage
	Pulmonary alveolar haemorrhage
	Rectal haemorrhage
	Retinal haemorrhage
	Shock haemorrhagic
	Vaginal haemorrhage
	Vitreous haemorrhage
Hypomagnesaemia	Hypomagnesaemia
	Magnesium deficiency
Hypotension	Hypotension
	Orthostatic hypotension
Hypoxia	Hypoxia
	Oxygen saturation decreased
Infections - pathogen unspecified	Bronchitis
	Catheter bacteraemia
	Conjunctivitis
	Device related infection
	Diverticulitis
	Infection
	Large intestine infection
	Mastoiditis
	Mucosal infection
	Nasopharyngitis
	Neutropenic sepsis
	Otitis media
	Parotitis
	Peritonitis

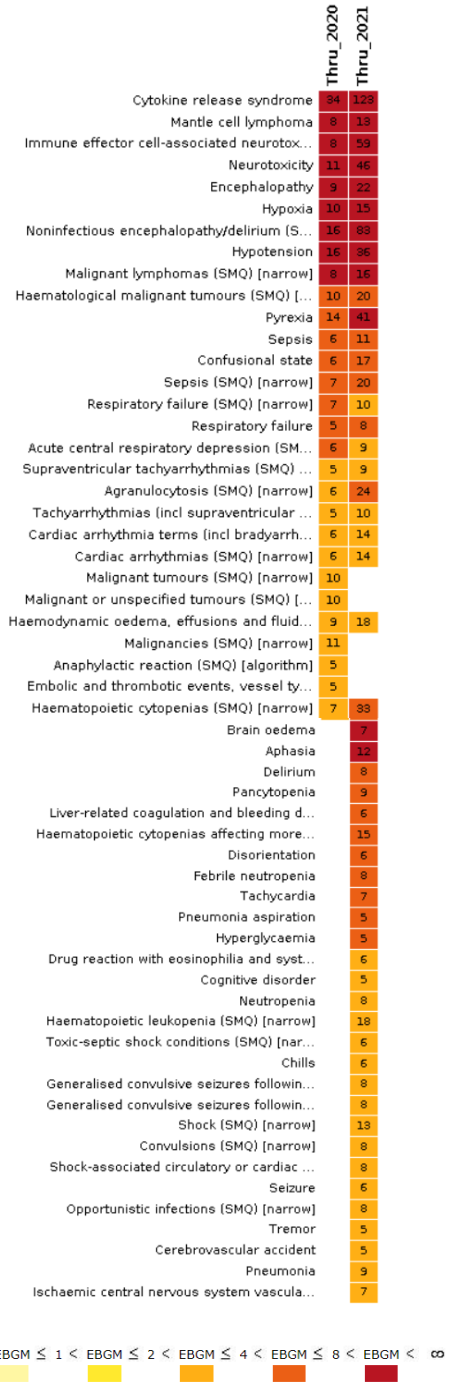
FDAGT*	AEDECOD**
	Pneumonia
	Pneumonia aspiration
	Sepsis
	Septic shock
	Sinusitis
	Skin infection
	Tooth infection
	Upper respiratory tract infection
	Urinary tract infection
	Vascular device infection
Leukocytosis	Leukocytosis
	White blood cell count increased
Leukopenia	Leukopenia
	White blood cell count decreased
Lymphopenia	Lymphocyte count decreased
	Lymphopenia
Musculoskeletal pain	Arthralgia
	Back pain
	Bone pain
	Coccydynia
	Muscle strain
	Musculoskeletal chest pain
	Musculoskeletal pain
	Myalgia
	Neck pain
	Non-cardiac chest pain
	Pain in extremity
Neutropenia	Neutropenia
	Neutrophil count decreased
Oedema	Face oedema
	Fluid overload
	Generalised oedema
	Gravitational oedema
	Localised oedema
	Oedema
	Oedema genital
	Oedema peripheral
	Penile oedema
	Periorbital oedema

FDAGT*	AEDECOD**
	Peripheral swelling
	Scrotal oedema
	Swelling face
	Tongue oedema
Paraesthesia	Dysaesthesia
	Paraesthesia
Peripheral neuropathy	Hypoaesthesia
	Intensive care unit acquired weakness
	Neuropathy peripheral
	Peripheral sensory neuropathy
	Peroneal nerve palsy
Pulmonary oedema	Pulmonary congestion*
	Pulmonary oedema
Rash	Catheter site erythema
	Catheter site urticaria
	Dermatitis bullous
	Dermatitis exfoliative generalised
	Drug eruption
	Erythema
	Infusion site pruritus
	Pruritus
	Rash
	Rash macular
	Rash maculo-papular
	Rash pustular
	Toxic skin eruption
	Urticaria
Renal impairment	Acute kidney injury
	Blood creatinine increased
	Renal failure
Respiratory failure	Acute respiratory failure
	Acute respiratory distress syndrome
	Respiratory distress
	Respiratory failure
Tachycardia	Sinus tachycardia
	Tachycardia
Thrombocytopenia	Platelet count decreased
	Thrombocytopenia
Thrombosis	Cerebral ischaemia

FDAGT*	AEDECOD**
	Deep vein thrombosis
	Device related thrombosis
	Embolism
	Optic ischaemic neuropathy
	Pulmonary embolism
	Splenic infarction
	Thrombosis
	Transient ischaemic attack
Viral infection	Cytomegalovirus viraemia
	Enterovirus infection
	Herpes simplex
	Herpes simplex viraemia
	Influenza
	Meningitis viral
	Metapneumovirus infection
	Oral herpes
	Parainfluenzae virus infection
	Pneumonia respiratory syncytial viral
	Pneumonia viral
	Respiratory syncytial virus infection
	Rhinovirus infection
	Viral upper respiratory tract infection
Visual impairment	Vision blurred
	Visual impairment

Source: FDA Analysis. ADAEFDA
*FDA grouped terms
**Preferred terms per ADAEFDA dataset

17.6. FDA - Empirica Signal Analysis



Source: FDA Analysis
Empirica Signal 16 August 2021 (MedDRA 24.0) using Selecti of 2 Dimensions, Pattern: PAM (BREXUCABTAGENE AUTOLEUCEL) + PT or Narrow_Alg SMQ(PT); and Display Minimum N = 5.0, Minimum EBGM = 2.0, Minimum EB05 = 1.0.

18 Signatures

Najat Bouchkouj, MD Date: 01 October 2021

Donna Przepiorka, MD, PhD Date: 01 October 2021

Bindu George, MD Date: 01 October 2021

Marc Theoret, MD Date: 01 October 2021

Tejashri Purohit-Sheth, MD Date: 01 October 2021