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Clinical Pharmacology BLA Review
Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissues and Advanced Therapy

BLA	125703/91
Product	TECARTUS (brexucabtagene autoleucel, KTE-X19), Cell suspension for intravenous infusion
Sponsor	Kite Pharma, Inc.
Indication	Treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (B-ALL)
Date Received	April 01, 2021
Reviewer	Xiaofei Wang, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation and Pharmacology/Toxicology
RPM	Crystal Melendez
Through	Tejashri Purohit-Sheth, M.D., FACAAI, CQIA Director Division of Clinical Evaluation and Pharmacology/Toxicology

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Table of Contents

1 EXECUTIVE SUMMARY

On April 01, 2021, Kite Pharma Inc. submitted a Prior Approval Supplement (PAS) seeking registration of TECARTUS (brexucabtagene autoleucel, KTE-X19) for the treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (B-ALL). The proposed dosing regimen is 1.0 x 10^6 CAR-positive viable T cells per kg body weight, with a maximum of 1.0 x 10^8 CAR-positive viable T cells to be infused intravenously in adult patients.

TECARTUS was approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (r/r MCL) on July 24, 2020.

The clinical pharmacology section of this PAS is supported by one Phase 1/2, multicenter, open-label study that evaluated the safety, efficacy, pharmacokinetics and pharmacodynamics of TECARTUS (KTE-X19) in adult patients with relapsed/refractory (r/r) B-cell precursor acute lymphoblastic leukemia (B-ALL) (Study # KTE-C19-03, ZUMA-3).

The proposed dosing regimen for TECARTUS administered by intravenous (IV) infusion has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable in subjects with r/r ALL. From a clinical pharmacology standpoint, the PAS is acceptable to support approval for the additional indication.

2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Following are the key clinical pharmacology findings of TECARTUS (KTE-X19) in adult subjects with B-cell precursor acute lymphoblastic leukemia (ALL):

- Following infusion, KTE-X19 exhibited an initial rapid expansion phase followed by a bi-phasic decline. Within the anti-CD19 CAR T dose range of 0.5 x 10^6 to 2.0 x 10^6 anti-CD19 CAR T cells/kg, there is no clear dose-response for KTE-X19 exposure (Cmax and $AUC_{0\text{-}28d}$). Median expansion (Cmax and $AUC_{0\text{-}28d}$) of KTE-X19 was highest in subjects treated at the 1.0 x 10^6 dose level with earlier intervention with corticosteroids (modified toxicity management).
- At the anti-CD19 CAR T dose level of 1x 10^6 cells/kg with modified toxicity management (earlier intervention with corticosteroids), following infusion, KTE-X19 exhibited an initial rapid expansion phase achieving maximal expansion (Cmax) around Day 15 followed by a bi-phasic decline.
- KTE-X19 was present in peripheral blood up to 18 months post-infusion in peripheral blood at the time of the data cutoff date, demonstrating long term persistence of KTE-X19.

- Multivariate analysis indicated that lower blast percentage in bone marrow at screening and higher (b) (4) were potentially associated with higher KTE-X19 expansion.

- Subjects with overall MRD negative status during the study had substantially higher KTE-X19 expansion, compared to subjects with in overall MRD positive status. Due to the small sample size, the results need to be interpreted with caution and no definitive conclusions be made.

- Substantially higher KTE-X19 expansion was observed in responding subjects (CR + CRi), compared to non-responding (non-CR/CRi) subjects. Higher KTE-X19 expansion was positively associated with best overall response (BOR) rate.

- Higher KTE-X19 exposure was associated with Grade 2 or higher cytokine release syndrome (CRS). Median Cmax and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects with Grade 2 or higher CRS were 7.9- and 5.8-fold higher, respectively, compared to subjects with Grade 1 or no CRS.

- Higher KTE-X19 exposure was associated with Grade 2 or higher neurological events. Median of Cmax and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects with Grade 2 or higher neurological events were 6.0- and 3.0-fold higher, respectively, compared to subjects with Grade 1 or no neurological events.

- Tocilizumab and corticosteroids were used in the management of CRS and neurologic events, respectively, after treatment with KTE-X19. Higher KTE-X19 expansion (Cmax and $AUC_{0\text{-}28d}$) was observed in subjects administered tocilizumab and/or corticosteroids compared to subjects who did not take tocilizumab or corticosteroids. KTE-X19 continued to expand in subjects who received tocilizumab and corticosteroids after infusion of KTE-X19.

- Substantially elevated levels were reported in subjects who developed severe (Grade 3 or higher) CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following serum biomarkers: ferritin, granzyme B, IFN-γ, IL-2Rα, IL-6, IL-8, IL-10, IL-15, TNF-α, and GM-CSF.

- Substantially elevated levels were reported in subjects who developed severe (Grade 3 or higher) neurological events compared to subjects with Grade 2, Grade 1 or no neurological events for the following serum biomarkers: IL-1RA and IL-6.

- KTE-X19 induced B-cell aplasia in majority of the treated subjects. At 12 months post KTE-X19 infusion, the B-cell levels recovered in 100% of evaluable subjects.

- Based on results of a confirmatory cell-based assay, five subjects treated with KTE-X19 had positive results against single chain variable region fragment (scFv) in CAR at time points no earlier than 3 months after infusion. There is no evidence that the kinetics of initial expansion and persistence of KTE-X19 was altered in these subjects.

- There was no reported presence of replication-competent retrovirus (RCR) in the blood of KTE-X19 treated subjects.

3 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125703/91 and finds it acceptable pending the following revisions shown below.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

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

12.2. Pharmacodynamics

After TECARTUS infusion, pharmacodynamic responses were evaluated over a four-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was generally observed within 8 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target effect of TECARTUS, a period of B cell aplasia is expected.

12.3. Pharmacokinetics

Following infusion (target dose of 2×10^6 anti-CD19 CAR T cells/kg) of TECARTUS in ZUMA-2, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by three months. Peak levels of anti-CD19 CAR T cells occurred within the first 15 days after TECARTUS infusion. Following infusion (target dose of 1 x 10^6 anti-CD19 CAR T cells/kg) of TECARTUS in ZUMA-3 (Phase 2), anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 6 months. Median anti-CD19 CAR T-cell time to peak was 15 days after TECARTUS infusion.

Description of Pharmacokinetics in Adult r/r MCL

The number of anti-CD19 CAR T cells in blood was associated with objective response [complete remission (CR) or partial remission (PR)]. Median peak anti-CD19 CAR T cell level in responders was 102.4 cells/μL (range: 0.2 to 2589.5 cells/μL; n = 51), and in nonresponders was 12.0 cells/μL (range: 0.2 to 1364.0 cells/μL, n = 8). The median $AUC_{Day\ 0\text{-}28}$ in patients with

an objective response was 1487.0 cells/µL•days (range: 3.8 to 2.77E+04 cells/µL•days; n = 51) versus 169.5 cells/µL•days in nonresponders (range: 1.8 to 1.17E+04 cells/µL•days; n = 8).

Median peak anti-CD19 CAR T-cell and AUC_{0-28} levels in patients who received neither corticosteroids nor tocilizumab (peak: 24.7 cells/µL; AUC_{0-28}: 360.4 cells/µL•days, n = 18) was similar to patients who received corticosteroids alone (peak: 24.2 cells/µL; AUC_{0-28}: 367.8 cells/µL•days, n = 2); both groups were lower than patients who received tocilizumab alone (peak: 86.5 cells/µL; AUC_{0-28}: 1188.9 cells/µL•days, n = 10); the highest exposure was in patients who received both corticosteroids and tocilizumab (peak: 167.2 cells/µL; AUC_{0-28}: 1996.0 cells/µL•days, n = 37).

Median peak anti-CD19 CAR T-cell values were 74.1 cells/µL in patients ≥ 65 years of age (n = 39) and 112.5 cells/µL in patients < 65 years of age (n = 28). Median anti-CD19 CAR T-cell $AUC_{Day\ 0-28}$ values were 876.5 cells/µL•day in patients ≥ 65 years of age and 1640.2 cells/µL•day in patients < 65 years of age.

Gender had no significant impact on $AUC_{Day\ 0-28}$ and C_{max} of TECARTUS.

Description of Pharmacokinetics in Adult r/r B-cell precursor ALL

Reviewer's Comments:

Results were updated based on clinical reviewer's efficacy assessment related to presentation of data with limitation to one decimal for PK parameters.

The following comments were conveyed to the Applicant:

Please update PK parameters information in subjects used tocilizumab and/or corticosteroids and subjects who did not use tocilizumab and/or corticosteroids based on your updated submission on 07/30/2021).

Suggest removing the paragraph about age and KTE-X19 expansion for following reasons:

1. *Small sample size for subjects ≥ 65 years of age.*
2. *Considering impact from other confounding factors. Multivariate logistic regression analysis was conducted evaluating potential factors impacting KTE-X19 expansion: product characteristics, patient demographic and baseline characteristics. Multivariate analysis indicated other product characteristics and patient baseline characteristics, but not age, were associated with KTE-X19 expansion.*

Based on above, it's premature to conclude age (≥ 65 years of age) is associated with higher KTE-X19 expansion at current stage.

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 = ~~36~~ 32) in patients who had overall complete remission (CR+CRi), and 0.49 cells/µL (range: 0.00 to 183.50 cells/µL, n = ~~14~~

17) in patients who had non-complete remission. The median AUC_{0-28} in patients who had overall complete remission (CR+CRi) was 424.03 cells/µL•days (range: 14.12 to 19,390.42 cells/µL•days; n = ~~36~~ 32) vs ~~4.12~~ 7.9 cells/µL•days in patients who had non-complete remission (range: 0.00 to ~~642.25~~ 889.0 cells/µL•days; n=~~14~~ 17).

Median peak anti-CD19 CAR T-cell and AUC_{0-28} levels in patients who received neither corticosteroids nor tocilizumab (peak ~~13.1~~ 5.7 cells/µL; AUC_{0-28}: ~~137.7~~ 60.7 cells/µL•days, n=~~7~~ 11) was higher than patients who received corticosteroids alone (peak: ~~0.0~~ 36.2 cells/ µL; AUC_{0-28}: ~~0.0~~ 423.1 cells/µL•days, n= 4 1); both groups were lower than evaluable patients who received tocilizumab alone (peak ~~20.9~~ 11.2 cells/ µL; AUC_{0-28}: ~~240.8~~ 137.4 cells/µL•days, n=~~6~~ 9); the highest exposure was in evaluable patients who received both corticosteroids and tocilzumab (peak: ~~34.8~~ 49.2 cells/µL; AUC_{0-28}: ~~398.9~~ 454.1 cells/ µL•days, n=~~33~~ 34).

Median peak anti-CD19 CAR T-cell levels were 34.8 cells/µL in evaluable patients ≥ 65 years of age (n=7) and 17.4 cells/µL in evaluable patients < 65 years of age (n = 43). Median anti-CD 19 CAR T-cell $AUC_{Day\ 0-28}$ values were 425.0 cells/µL•day in patients ≥ 65 years of age and 137.7 cells/µL•day in patients < 65 years of age.

Hepatic and renal impairment studies of TECARTUS were not conducted.

4 RECOMMENDATIONS

The clinical pharmacology information in this BLA supplement is acceptable, provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in Section 12 of the package insert. Please refer to Section 3 for detailed Labeling Recommendations.

5 APPENDIX - INDIVIDUAL STUDY

5.1 Study #1

5.1.1 Study Design

Study Title: A Phase 1/2 multicenter study evaluating the safety and efficacy of KTE-X19[1] in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) (Study No. KTE-C19-103, ZUMA-3)

Clinical Pharmacology Objectives and Endpoints

Category	Pharmacokinetics	Pharmacodynamics	Exploratory
Objectives	To assess levels of anti-CD19 CAR T cells in blood	• To assess the levels of cytokines in serum • To assess levels of B cells over time	• To investigate associations among pharmacokinetics, pharmacodynamics, efficacy, and safety outcomes • To characterize the preinfusion KTE-X19 product and investigate associations with pharmacokinetics, efficacy, and safety outcomes
Endpoints	Levels of anti-CD19 CAR T cells in blood	• Levels of cytokines in serum • Levels of B cells over time	• Associations of pharmacokinetics, pharmacodynamics, efficacy, and safety outcomes • Preinfusion product characteristics and their associations with pharmacokinetics, efficacy, and safety outcomes

Abbreviations: CAR, chimeric antigen receptor.

Source: Applicant. ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Table 1.

Study Design

ZUMA-3 is a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r B-ALL. Figure 1 shows subject treatment schema.

As of the data cutoff date of September 09, 2020, a total of 45 subjects were treated in the dose-finding Phase 1 portion across the following cohorts in order of enrollment:

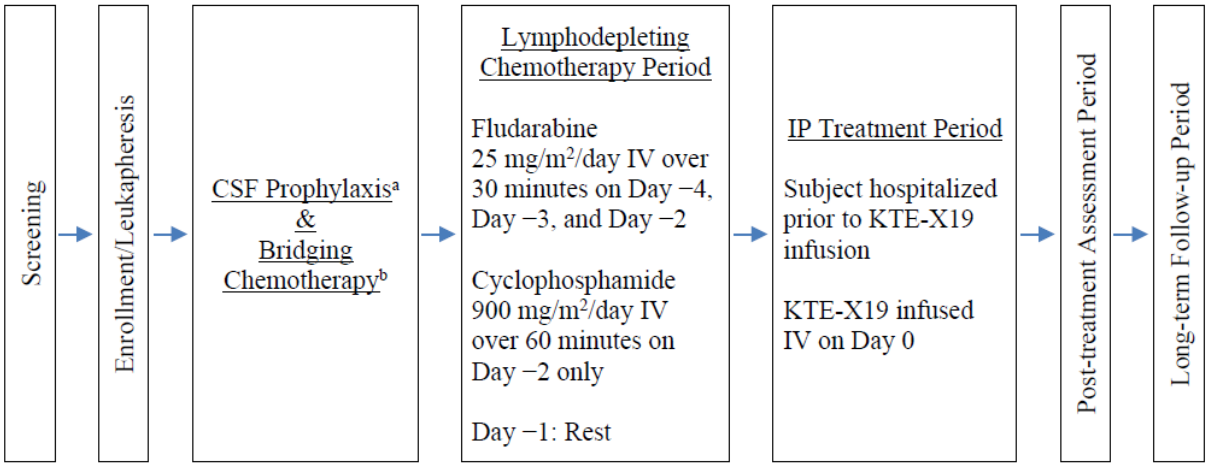
- 2 x 10^6 anti-CD19 CAR T cells/kg dose level (2e6 dose level) (n=6)
- 1 x 10^6 anti-CD19 CAR T cells/kg dose level (1e6 dose level) (n=14)

[1] In this review, TECARTUS is referred to as KTE-X19.

- 0.5 x 10^6 anti-CD19 CAR T cells/kg dose level with a product volume of 68 mL (0.5e6 dose level/68 mL) (n=9)
- 0.5 x 10^6 anti-CD19 CAR T cells/kg dose level with a product volume of 40 mL (0.5e6 dose level/40mL) (n=7)
- 1 x 10^6 anti-CD19 CAR T cells/kg dose level with modified toxicity management (1e6 dose level with modified toxicity management) (n=9)

The safety profile observed in subjects who received the 1 x 10^6 anti-CD19 CAR T cells/kg dose[2] and earlier intervention with corticosteroids (modified toxicity management) was considered 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. A total of 55 subjects were treated at 1 x 10^6 anti-CD19 CAR T cells/kg dose according to the modified toxicity management guidance.

Figure 1. Subject Treatment Schema – ZUMA-3 Phase 1 & Phase 2



Abbreviations: CSF, cerebrospinal fluid; IP, investigational product; IV, intravenous.

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/mm³ in the peripheral circulation).

Source: Applicant. ZUMA-3 Clinical Study Report (ZUMA-3): Figure 1.

[2] In this review, 1 x 10^6 anti-CD19 CAR T cells/kg dose is referred to as 1e6 dose.

Table 1 lists the sampling time points and bioanalytical methods for pharmacokinetic (PK) and pharmacodynamic (PD) assessments.

Table 1. Pharmacokinetic and Pharmacodynamic Methods (ZUMA-3)

Category/Method	Description
Pharmacokinetics	
PBMC sampling times	• At enrollment/leukapheresis • Day 0[a] • After infusion on Days 7, 14, 28, Month 3, then every 3 months through Month 24 and annually thereafter • At unscheduled hospital readmission with any KTE-X19-related AEs, then weekly, and on day of discharge • At the time of disease progression
Assays	
Assay for anti-CD19 CAR T cells in PBMC by (b) (4)	Qualified (b) (4) method (b) (4) for levels of anti-CD19 CAR T cells in PBMC; see m5.3.1.4
Harmonization of (b) (4) method for PK Monitoring in ZUMA-1 and ZUMA-2	PK data derivation method alignment between (b) (4) and (b) (4) reporting data as anti-CD19 CAR T cells/µl of blood

Abbreviations: AE, adverse event; BED, business enabling document; CAR, chimeric antigen receptor; (b) (4) (b) (4) PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic; REP, report.
a The Day 0 time point was taken before KTE-X19 infusion.

Category/Method	Description
Serum Analytes	
Serum sampling times	• At enrollment/leukapheresis • At Day 0[a] • After infusion on Days 3, 7, 14 and 28 • At unscheduled hospital readmission with any KTE-X19-related AEs, then weekly, and on day of discharge • At the time of disease progression
Assays	
(b) (4)	

5.1.2 Results

5.1.2.1 Pharmacokinetics

General Pharmacokinetic Characteristics for All Treated Subjects

With the data cut-off date of September 9, 2020, a total of 100 (45 subjects in the Phase 1 dose-finding portion and 55 subjects in Phase 2) were treated with KTE-X19 in Study ZUMA-3.

Dose-Exposure Relationship (Phase 1)

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. Table 2 shows a summary of PK parameters of KTE-X19 in blood of different dose cohorts in the Phase 1. Within the anti-CD19 CAR T cells/kg dose range of 0.5 x 10^6 to 2.0 x 10^6, there is no clear dose-response for KTE-X19 exposure (Cmax and $AUC_{0\text{-}28d}$). 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 $AUC_{0\text{-}28d}$.

Table 2. Summary of Anti-CD19 CAR T-cell Peak and $AUC_{0\text{-}28d}$ in Blood by Dose Cohort

	Phase 1					
	2e6 (N = 6)	1e6[a] (N = 14)	0.5e6 (68 mL) (N = 9)	0.5e6 (40 mL) (N = 7)	1e6[b] (N = 9)	Total (N = 45)
Peak (cells/µL)						
n	3	9	9	6	7	34
Mean (STDEV)	9.60 (9.58)	350.03 (911.79)	75.31 (108.80)	59.10 (127.78)	45.30 (29.05)	133.19 (474.14)
Median (Q1, Q3)	8.55 (0.59, 19.66)	26.54 (19.84, 50.12)	23.11 (6.73, 82.06)	4.69 (0.00, 26.12)	37.70 (17.82, 79.94)	22.50 (7.57, 53.05)
Min, max	0.59, 19.66	9.55, 2,776.95	0.17, 303.93	0.00, 319.12	7.57, 83.99	0.00, 2,776.95
$AUC_{0\text{-}28}$ (cells/µL•days)						
n	3	9	9	6	7	34
Mean (STDEV)	165.26 (184.63)	2,642.40 (6,688.83)	708.55 (943.28)	448.32 (894.75)	491.41 (374.28)	1,081.88 (3,483.70)
Median (Q1, Q3)	118.84 (8.27, 368.67)	338.38 (202.75, 559.15)	170.05 (65.17, 840.24)	64.77 (0.00, 301.81)	485.63 (139.18, 780.03)	205.55 (112.91, 604.62)
Min, max	8.27, 368.67	112.91, 20,450.90	1.82, 2,322.46	0.00, 2,258.56	131.96, 1,122.59	0.00, 20,450.90
Time-to-Peak (Days)						
n	3	9	9	6	7	34
Mean (STDEV)	20.33 (9.24)	11.22 (3.63)	12.67 (6.91)	12.67 (8.82)	11.29 (4.15)	12.68 (6.42)
Median (Q1, Q3)	15 (15, 31)	9 (8, 15)	9 (8, 15)	8 (8, 14)	8 (8, 15)	9 (8, 15)
Min, max	15, 31	8, 16	7, 29	8, 30	8, 17	7, 31

Data cutoff date = 09SEP2020
Abbreviations: AUC, area-under-the-curve; CAR, chimeric antigen receptor; max, maximum; min, minimum; Q, quartile; STDEV, standard deviation.
$AUC_{0\text{-}28}$ 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.
Peak is defined as the maximum number of CAR T cells in blood measured after infusion.
Time-to-peak is defined as the number of days from KTE-C19 infusion to the date when the number of CAR T cells in blood first reached the maximum post-baseline level.
2e6 = 2 x 10^6 anti-CD19 CAR T cells/kg; 1e6 = 1 x 10^6 anti-CD19 CAR T cells/kg; 0.5e6 = 0.5 x 10^6 anti-CD19 CAR T cells/kg
a 1e6 dose cohort with original toxicity management.
b 1e6 dose cohort with modified toxicity management.

Source: Applicant. ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Table 5.

Pharmacokinetics of 1x 10^6 anti-CD19 CAR T cells/kg

All subjects in Phase 2 were treated with KTE-X19 at 1e6 dose level 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 $AUC_{0\text{-}28d}$ for subjects in Phase 2 were 20.6 cells/µL and 220.60 cells/µL*days, respectively. Medina Tmax was 15 days post-dose.

Table 3. Summary of KTE-X19 Pharmacokinetic Parameters in Blood

	Phase 2 (N = 55)	**Combined Phase 1 and Phase 2 1e6 Dose Cohorts (N = 78)**
Peak (cells/µL)		
n	50	66
Mean (STDEV)	74.98 (220.53)	109.33 (385.27)
Median (Q1, Q3)	20.62 (4.58, 62.97)	24.31 (5.97, 62.97)
Min, max	0.00, 1,533.40	0.00, 2,776.95
$AUC_{0\text{-}28}$ (cells/µL•days)		
n	50	66
Mean (STDEV)	847.74 (2,751.89)	1,054.67 (3,412.39)
Median (Q1, Q3)	220.60 (56.25, 676.94)	242.90 (82.12, 676.94)
Min, max	0.00, 19,390.42	0.00, 20,450.90
Time-to-Peak (Days)		
n	50	66
Mean (STDEV)	15.54 (6.78)	14.50 (6.42)
Median (Q1, Q3)	15 (11, 16)	15 (8, 15)
Min, max	7, 32	7, 32

Source: Applicant. ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Table 6.

At dose level of 1e6 cells/kg, KTE-X19 was detectable in 2 of 7 evaluable adult subjects with r/r ALL up to 18 months in peripheral blood at the time of the data cutoff date.

Factors Impacting KTE-X19 Pharmacokinetics

Analysis was conducted to explore potential factors that may have impacted KTE-X19 pharmacokinetics with clinical reviewer's safety analysis set (subjects at 1e6 dose level in Study ZUMA-3). Subject demographic characteristics, baseline characteristics, and product characteristics were evaluated for potential associations with KTE-X19 cellular kinetics/pharmacokinetics.

Univariate analysis showed that elderly subjects (≥ 65 years of age), lower blast percentage in bone marrow at screening, lower B-ALL CD19 expression levels at baseline, and higher (b) (4) (b) (4) may potentially be associated with higher KTE-X19 expansion. Additional multivariate analysis was conducted for above potential factors. Results from multivariate analysis indicated that lower blast percentage in bone marrow at screening and higher (b) (4) (b) (4) were potentially associated with higher KTE-X19 expansion (Table 4).

Table 4. Summary of Multivariate Logistic Regression for Potential Impact Factors for KTE-X19 Expansion

	Estimate	Std. Error	P value
LOGCmax			
Intercept	-1.806e-01	1.76	0.9189
Age ((≥ 65 years of age)	3.461e-01	2.608e-01	0.1934
Blast percentage in bone marrow at screening	-1.328e-02	5.625e-03	0.0241*
B-ALL CD19 expression at baseline	5.963e-03	1.625e-02	0.7159
(b) (4)	(b) (4)	(b) (4)	(b) (4)
LOGAUC$_{0\text{-}28d}$			
Intercept	4.489e-01	2.169	0.8373
Age ((≥ 65 years of age)	3.960e-01	3.214e-01	0.2264
Blast percentage in bone marrow at screening	-1.791e-02	6.932e-03	0.0142*
B-ALL CD19 expression at baseline	1.004e-02	2.003e-02	0.6192
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Source: FDA's analysis.

Tocilizumab and Corticosteroids on KTE-X19 Pharmacokinetics

Tocilizumab and corticosteroids were used in the management of cytokine release syndrome (CRS) and neurologic events.

In Phase 2, the Cmax and $AUC_{0\text{-}28d}$ in subjects treated with both tocilizumab and corticosteroids (n=34) were about 8.6- and 7.5-fold of that in subjects who received neither tocilizumab or corticosteroids (n=11) (Table 5). Subjects treated with tocilizumab only (n=9) or corticosteroids only (n=1) also had substantially higher KTE-X19 exposure than subjects who received neither tocilizumab or corticosteroids (n=11). 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. KTE-X19 cells continued to expand in subjects who received tocilizumab and corticosteroids after infusion of KTE-X19.

Table 5 KTE-X19 Expansion by Tocilizumab and Corticosteroids Administration

Median (Min, Max)	**Tocilizumab + Corticosteroids Treatment (N=34)**	**Tocilizumab Treatment Only (N=9)**	**Corticosteroids Treatment Only (N=1)**	**No Tocilizumab + Corticosteroids Treatment (N=11)**
Cmax (cells/μL)	49.2 (0.6, 1533.4)	11.2 (0.0, 86.8)	36.2 (36.2, 36.2)	5.7 (0.0, 46.7)
Tmax (days)	15.0 (8.0, 32.0)	11.5 (8.0, 29.0	14.0 (14.0, 14.0)	15.0 (7.0, 29.0)
$AUC_{0\text{-}28d}$ (days*cells/μL)	454.1 (7.9, 19390.4)	137.4 (0.0, 693.0)	423.1 (423.1, 423.1)	60.7 (0.0, 508.1)

Source: FDA's analysis.

5.1.2.2 Pharmacodynamics

Serum Biomarkers

A panel of serum biomarkers (47 in Phase and 40 in Phase 2) were monitored longitudinally till 4 weeks post-infusion of KTE-X19. A subset of 18 homeostatic, inflammatory, and immune-modulating cytokines, chemokines and immune effector molecules were preselected for detailed examination.

Among ZUMA-3 study subjects, after lymphodepleting chemotherapy, median serum levels of homeostatic cytokines IL-7 and IL-15 were elevated at least 2-fold and median serum levels of perforin decreased by at least 2-fold relative to baseline. After KTE-X19 infusion, serum levels of IFN-γ, IL-2, IL-6, IL-7, IL-10, and IL-15 increased to at least 2-fold relative to baseline at Day 3. Serum levels of perforin continued to decrease on Day 3. Majority key analytes achieved peak levels at around 8 days (range: 7-8 days), except perforin (median Tmax was 15 days). Most analytes were elevated by ≥ 2-fold at peak compared with baseline in ≥ 50% of subjects

(exceptions: ICAM-1, perforin, and VCAM-1) Serum perforin concentrations decreased after lymphodepletion till Day 3 after infusion, and then increased to peak levels around 15 days post-infusion. By Week 4, majority of the preselected analytes returned to near or below baseline levels; except following 7 analytes remained elevated by ≥ 2-fold in ≥ 20% of subjects: CXCL10, IFN-γ, IL-1RA, IL-6, IL-7, IL-10, and IL-15).

The applicant conducted correlative analysis to explore potential associations between serum biomarkers and adverse events such as CRS and neurological events. The following potential associations were observed (nominal Wilcoxon rank sum test p-value ≤0.05):

Severe CRS (Grade 3 or higher) versus Grade 2 or lower or no CRS:

- Median peak serum levels for the following analytes were numerically higher among subjects who experienced worst Grade 3 or higher CRS than those who experienced worst Grade 2, worst Grade 1, or no CRS after infusion of KTE-X19: ferritin, granzyme B, IFN-γ, IL-2Rα, IL-6, IL-8, IL-10, IL-15, TNF-α, and GM-CSF.
- Serum analytes with nominally significant p-values for association of median AUC with worst Grade 3 or higher CRS compared with worst Grade 2, worst Grade 1, or no CRS were IL-2Rα (p = 0.0082), IL-15 (p = 0.0316), IL-7 (p = 0.0366).

Grade 2 or higher CRS versus Grade 1 or no CRS:

- Median peak serum levels for the following analytes were numerically higher among subjects who experienced worst Grade 2 or higher CRS than those who experienced worst Grade 1 or no CRS after infusion of KTEX19: IFN-γ, IL-1RA, IL-2, IL-6, IL-8, IL-10, and IL-15.
- Serum analytes with nominally significant p-values for association of median AUC with worst Grade 2 or higher CRS compared with worst Grade 1 or no CRS were IFN-γ (p = 0.0031), IL-15 (p = 0.0123), IL-2 (p = 0.0166), IL-6 (p = 0.0387).

Severe neurological events (Grade 3 or higher) versus Grade 2 or lower or no neurological events:

- Median peak serum levels for the following analytes were numerically higher among subjects who experienced worst Grade 3 or higher neurologic AEs than those who experienced worst Grade 2, worst Grade 1, or no neurologic AEs after infusion of KTE-X19: IL-1RA and IL-6.
- Median AUC for the following analytes were numerically higher among subjects who experienced worst Grade 3 or higher neurologic AEs than those who experienced worst Grade 2, worst Grade 1, or no neurologic AEs after infusion of KTE-X19: IL-1RA.

Grade 2 or higher neurological events versus Grade 1 or no neurological events:

- Median peak serum levels for the following analytes were numerically higher among subjects who experienced worst Grade 2 or higher neurologic AEs than those who experienced worst Grade 1 or no neurologic AEs after infusion of KTE-X19: IFN-γ, IL-1RA, IL-2Rα, and IL-10.
- Serum analytes with nominally significant p-values for association of median AUC with worst Grade 2 or higher neurologic AEs compared with worst Grade 1 or no neurologic

AEs were IL-1RA (p = 0.0013), IL-10 (p = 0.0113), IFN-γ (p = 0.0136), granzyme B (p = 0.0286), ferritin (p = 0.0332), and IL-15 (p = 0.0361).

B-Cell Aplasia

Treatment of KTE-X19 may induce B-cell aplasia. The incidence of B-cell aplasia was assessed. In Study ZUMA-3, majority of the subjects (100% in Phase 1 and 95.9% in Phase 2) had detectable B cells at baseline. The median B-cell percentage in PBMC were 43.2% and 22.7% for Phase 1 and Phase 2, respectively. At Day 28 post-KTE-X19 infusion, the percentage of subjects with detectable B cells decreased to 52% and 25% for Phase 1 and Phase 2, respectively. The median B cell percentage in PBMC also decreased substantially to 0.40% and 0.05% for Phase 1 and Phase 2, respectively. At 12 months post KTE-X19 infusion, 100% evaluable subjects had detectable B-cells. The median B cell percentage were 13.9% for Phase 1 and 20.1% for Phase 2.

5.1.2.3 Exposure-Response Relationship

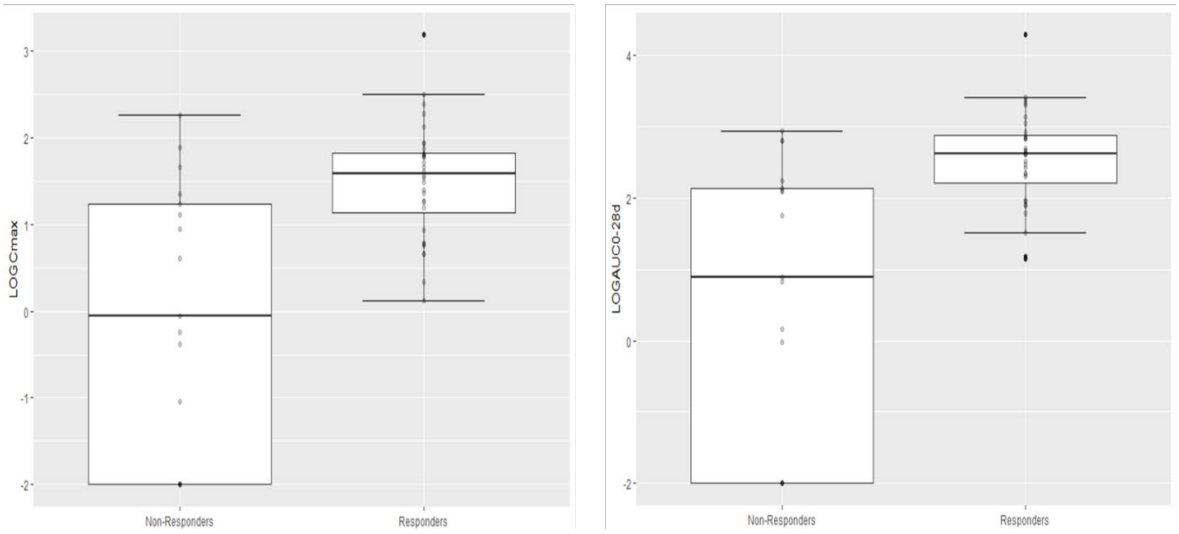
Exposure-Response for Efficacy

Exposure and Best Overall Response (BOR)

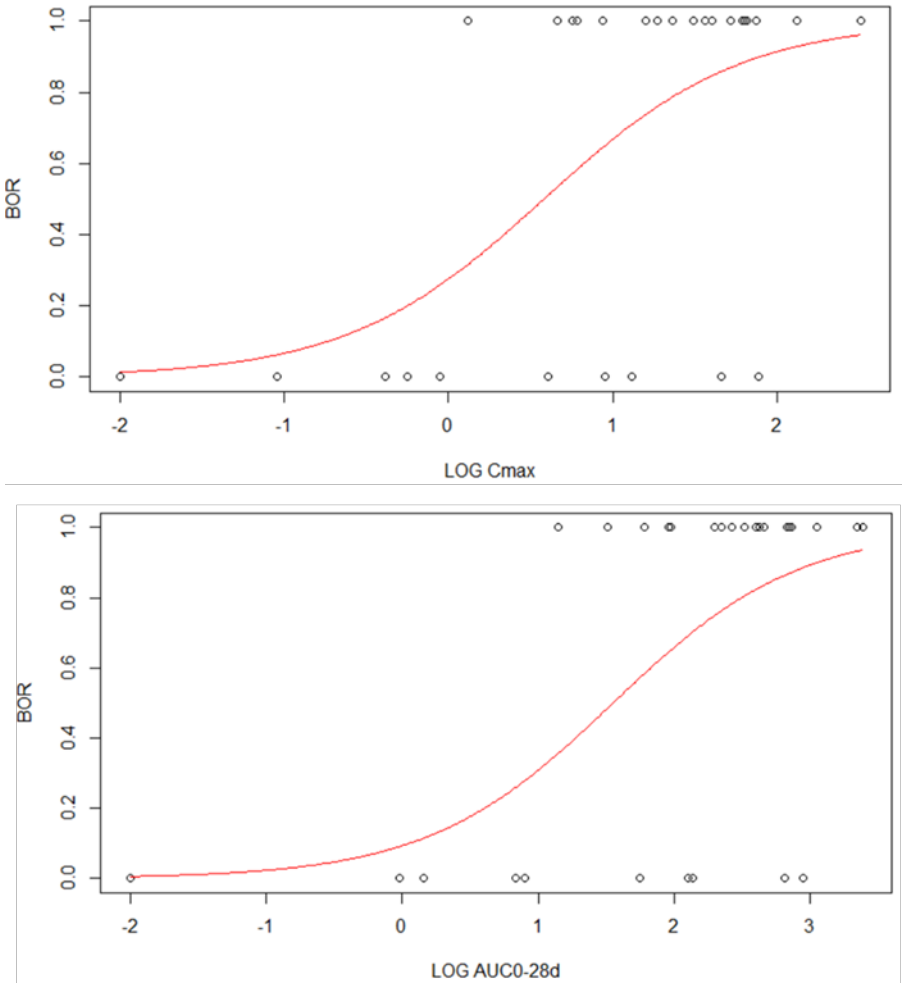
The relationship between KTE-X19 exposure and efficacy was based on results of clinical reviewer's best overall response (BOR) assessment for the ZUMA-3 Phase 2 subject population. As shown in Figure 2 and Table 6, KTE-X19 expansions in responding subjects [complete remission (CR) and complete remission with incomplete hematologic recovery (CRi)] were substantially higher than that in non-responding (non-complete remission) subjects.

Figure 2. KTE-X19 Expansion and Best Overall Response

a. Boxplot



b. Univariate logistic analysis



Source: FDA's analysis.

Table 6. Comparison of KTE-X19 Expansion Between Responding and Non-responding Subjects

Parameters (Unit),	**Responding Subjects N=35**	**Non-Responding Subjects N=19**	**p-value***
Cmax [median (range)], (cells/µL)	38.4 (1.3, 1533.4) (n=32)	0.9 (0.0, 183.5) (n=17)	0.0006***
Tmax [median, range], (days)	15.0 (8.0, 30.0) (n=32)	15.0 (7.0, 32.0) (n=17)	-
$AUC_{0\text{-}28d}$ [median (range)], (days*cells/ µL)	424.0 (14.1, 19390.4) (n=32)	7.9 (0.0, 889.0) (n=17)	0.00032***

* Wilcoxon rank sum test. *Source: FDA's analysis.*

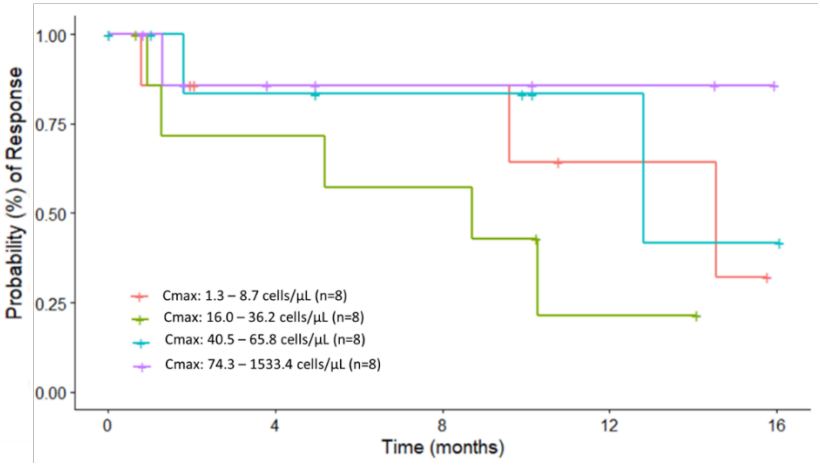
Multivariate logistic analysis was conducted to explore other potential confounding factors for KTE-X19 efficacy — BOR. Following factors were evaluated: KTE-X19 expansion (Cmax and $AUC_{0\text{-}28d}$), subjects' demographic characteristics, subjects' baseline characteristics, and product characteristics. Except for KTE-X19 expansion (Cmax and $AUC_{0\text{-}28d}$), no other factors were identified to be potentially associated with KTE-X19 efficacy outcomes (BOR).

Exposure and Duration of Response (DOR)

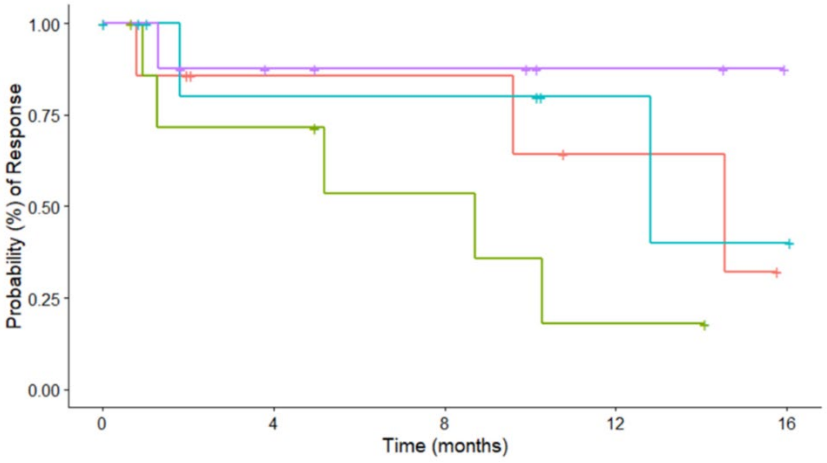
Figure 3 shows Kaplan-Meier curves of duration of response (DOR) by quantile analysis of KTE-X19 exposure (Cmax and $AUC_{0\text{-}28d}$). Subjects with the highest quantile of KTE-X19 exposure appeared to have longer DOR than subjects in other groups. However, Cox Proportional-Hazard analysis did not show significant correlation between KTE-X19 exposure and DOR.

Figure 3. Kaplan-Meier Curve of Duration of Response (DOR) by KTE-X19 Exposure Quantile Groups

a. Cmax



b. $AUC_{0\text{-}28d}$



Source: FDA's analysis.

Exposure and Minimal Residual Disease (MRD) Status

Among the 46 subjects in Phase 2 with evaluable bone marrow samples, 4 subjects were MRD^+ and 42 subjects were MRD^- at Month 1, 2, or 3. Subjects with negative MRD (MRD^-) status had substantially higher KTE-X19 expansion, compared to subjects with positive MRD status (MRD^+). Median anti-CD19 CAR T-cell peak levels were higher in MRD^- subjects (31.0 cells/µL) relative to MRD^+ subjects (0.5 cells/µL). The median $AUC_{0\text{-}28d}$ was also higher in MRD^- subjects (329.8 cells/µL•days) relative to MRD^+ subjects (3.9 cells/µL•days) (Table 7).

At Week 4, there were 41 subjects had evaluable MRD status. Among the 38 subjects with MRD^- status, 36 subjects were responders (CR or CRi) at Week 4 and 2 subjects were non-CR/CRi. All 3 subjects with MRD^+ status were non-CR/CRi. KTE-X19 expansion was numerically higher in MRD^- subjects who were responders (CR or CRi) relative to MRD^- subjects who were non-CR/CRi and MRD^+ subjects (Table 8).

Due to the small sample size, the results need to be interpreted with caution.

Table 7. Summary of Anti-CD19 CAR T-cell Expansion (Cmax and $AUC_{0\text{-}28d}$) in Blood by Overall MRD Status in Bone Marrow

	MRD Status Overall in Bone Marrow Sample	
	Positive (N = 4)	Negative (N = 42)
Peak (cells/µL)		
n	4	39
Mean (STDEV)	5.85 (11.06)	89.23 (246.86)
Median (Q1, Q3)	0.49 (0.05, 11.65)	31.00 (6.04, 65.85)
Min, max	0.00, 22.43	0.57, 1,533.40
$AUC_{0\text{-}28}$ (cells/µL•days)		
n	4	39
Mean (STDEV)	45.26 (85.42)	1,048.34 (3,091.76)
Median (Q1, Q3)	3.87 (0.48, 90.05)	329.81 (90.53, 731.14)
Min, max	0.00, 173.31	7.91, 19,390.42

Source: Applicant. ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Table 20.

Table 8. Summary of Anti-CD19 CAR T-cell Expansion (Cmax and $AUC_{0\text{-}28d}$) in Blood (Cells/µL) by MRD Status in Bone Marrow at Week 4 Among CR/CRi and non-CR/CRi per Central Assessment

	MRD Status in Bone Marrow at Week 4			
	Negative (N = 38)		Positive (N = 3)	
	CR/CRi (N = 36)	Non-CR/CRi (N = 2)	CR/CRi (N = 0)	Non-CR/CRi (N = 3)
Peak (cells/µL)				
n	33	2	0	3
Mean (STDEV)	101.30 (267.00)	4.76 (5.94)		7.80 (12.67)
Median (Q1, Q3)	34.79 (8.67, 74.33)	4.76 (0.57, 8.96)		0.88 (0.09, 22.43)
Min, max	1.31, 1,533.40	0.57, 8.96		0.09, 22.43
$AUC_{0\text{-}28}$ (cells/µL•days)				
n	33	2	0	3
Mean (STDEV)	1,202.63 (3,344.53)	67.07 (83.65)		60.35 (97.87)
Median (Q1, Q3)	398.92 (93.73, 831.70)	67.07 (7.91, 126.22)		6.79 (0.95, 173.31)
Min, max	14.12, 19,390.42	7.91, 126.22		0.95, 173.31

Source: Applicant. ZUMA-3 Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report, Table 22.

Exposure-Response for Safety

Data from subjects at dose level of 1e6 with modified toxicity management was used to explore exposure-response for safety analysis.

Exposure and Cytokine Release Syndrome (CRS)

Impact of KTE-X19 exposure on cytokine release syndrome (CRS) was evaluated. Subjects with Grade 2 or higher CRS had substantial higher KTE-X19 exposure than subjects with Grade 1 or no CRS (Table 9). Univariate logistic regression analysis indicates potential positive associations between KTE-X19 exposure and probability of Grade 2 or higher CRS (Table 10). Higher KTE-X19 exposure (but not statistically significant) was observed in subjects with severe (Grade 3 or higher) CRS, compared to subjects with Grade 2, Grade 1 or no CRS. Similar results were obtained from analysis of 1e6 dose level data and Phase 2 data.

Table 9. Summary of KTE-X19 Expansion and Cytokine Release Syndrome

Parameters Median (range)	**Grade ≥ 2 (N=46)**	**Grade ≤ 1 (N=18)**	**p-value***
Cmax (cells/µL)	46.1 (0.0, 1533.4) (N=39)	5.8 (0.0, 86.8) (N=18)	0.0013**
$AUC_{0\text{-}28d}$ (days*cells/µL)	460.9 (0.0, 19390.4) (N=39)	79.2 (0.0, 693.0) (N=18)	0.00032***
Tmax (days)	15.0 [8.0, 32.0] (N=39)	15.0 (7.0, 29.0) (N=18)	--

*Wilcoxon rank sum test
Source: FDA's analysis.

Table 10. Logistic Regression Analysis on Association Between KTE-X19 Exposure and Incidence of Grade 2 or higher Cytokine Release Syndrome

Log Cmax			
	Odds Ratio	p value	95% CI of Odds Ratio
Intercept	0.99	0.9836	0.37 – 2.31
LogCmax	2.08	0.0237*	1.17 – 4.33
Log $AUC_{0\text{-}28d}$			
	Odds Ratio	p value	95% CI of Odds Ratio
Intercept	0.64	0.4726	0.16 – 1.91
Log$AUC_{0\text{-}28d}$	1.80	0.0309	1.12 – 3.39

Source: FDA's analysis.

Exposure and Neurological Events (NEs)

Potential associations between KTE-X19 and neurological events (NEs) were evaluated. Subjects with Grade 2 or higher NEs had higher KTE-X19 exposure than subjects with Grade 2, Grade 1 or no NEs (Table 11). Univariate logistic regression analysis indicates potential positive associations between KTE-X19 exposure and probability of Grade 2 or higher NEs (Table 12). Higher KTE-X19 exposure (but not statistically significant) was observed in subjects with severe (Grade 3 or higher) NEs, compared to subjects with Grade 2, Grade 1 or no NEs. Similar results were obtained from analysis of 1e6 dose level data and Phase 2 data.

Table 11. Summary of KTE-X19 Exposure and Neurological Events

Parameters Median (range)	**Grade ≥ 2 (N=41)**	**Grade ≤ 1 (N=23)**	**p-value***
Cmax (cell/µL)	81.8 (0.0, 1533.4) (N=39)	13.6 (0.0, 86.9) (N=18)	0.04338*
$AUC_{0\text{-}28d}$ (days*cells/µL)	398.9 (0.0, 19390.4) (N=39)	133.5 (0.0, 693.0) (N=18)	0.02088*
Tmax (days)	15.0 (8.0, 32.0) (N=39)	15.0 (7.0, 29.0) (N=18)	--

*Wilcoxon rank sum test
Source: FDA's analysis.

Table 12. Logistic Regression Analysis on Association Between KTE-X19 Exposure and Incidence of Grade 2 or higher Neurological Events

Log Cmax			
	Odds Ratio	p value	95% CI of Odds Ratio
Intercept	0.98	0.9625	0.36 – 2.29
LogCmax	2.11	0.0222*	1.18 – 4.43
Log $AUC_{0\text{-}28d}$			
	Odds Ratio	p value	95% CI of Odds Ratio
Intercept	-0.51	0.4221	0.13 – 1.82
Log$AUC_{0\text{-}28d}$	0.62	0.0263*	1.15 – 3.61

Source: FDA's analysis.

Exploration of Potential Confounding Factors for CRS and NEs

To explore other potential confounding factors for KTE-X19 safety (CRS and NEs), multivariate logistic analysis was conducted for CRS and NEs, respectively. Following factors were evaluated: KTE-X19 expansion (Cmax and $AUC_{0\text{-}28d}$), subjects' demographic characteristics, subjects' baseline characteristics, and product characteristics. Except for KTE-X19 expansion (Cmax and $AUC_{0\text{-}28d}$), no other factors were identified to be potentially associated with KTE-X19 safety outcomes (CRS and NEs).

5.1.2.4 Immunogenicity

The applicant performed immunogenicity assessment by monitoring the development of antibodies against the murine monoclonal antibody FMC63, the parent antibody from which the single chain variable region fragment (scFv) utilized in KTE-X19 is derived. The ELISA-based assays were first used to screen for the presence of antibodies against the murine antibody FMC63 (parent antibody from which the scFv of the anti-CD19 CAR is derived). Samples from subjects who had a positive ELISA result underwent further testing with a confirmatory cell-based assay to determine whether the positive signal observed in the ELISA was due to the antibody binding to a properly folded scFv expressed on the surface of an anti-CD19 CAR T cell.

In Phase 2, based on the initial screening ELISA, 3 subjects (5%) were antibody-positive at baseline, 1 subject (2%) was antibody negative at baseline and antibody-positive at Day 28 after the KTE-X19 infusion, and 1 re-treated subject was antibody positive at Day 28 after the KTE-X19 infusion. Samples from all above subjects were further assessed with a confirmatory cell-based (b) (4) assay. Results of the confirmatory assay demonstrated that all above subjects were antibody-negative at all time points tested.

In Phase 1, based on the initial screening ELISA, 6 subjects (13%) were antibody-positive at baseline, 5 subjects (11%) were antibody-negative at baseline and antibody-positive at any postbaseline time point, and 1 subject (2%) had no antibody testing at baseline and was antibody-positive at Day 28. Among these 12 subjects, 5 were confirmed to be antibody-positive in the confirmatory cell-based assay. All the 5 subjects were antibody-negative at baseline. One subject was antibody-positive at Month 3 after first infusion of KTE-X19 and were negative afterwards. Three subjects were tested antibody-positive at least 6 months after first infusion of KTE-X19. One subject was tested antibody-positive at Month 9 after first KTE-X19 treatment, antibody-positive after retreatment with KTE-X19 at Retreatment Day 28 and Retreatment Month 3.

In Study ZUMA-3, KTE-X19 cells exhibited an initial rapid expansion and reached peak levels in blood around 15 days post-infusion. Blood KTE-X19 cells levels declined to near baseline levels by 6 months. There is no evidence that the kinetics of initial expansion and persistence of KTE-X19 was altered in these subjects.

5.1.2.5 Replication-competent Retrovirus (RCR)

KTE-X19 comprises retroviral vector transduced T cells, the presence of replication-competent retrovirus (RCR) in the blood of treated subjects were monitored. RCR was not detected in any subjects post-KTE-X19 infusion.

5.1.3 Conclusions

Following are the key clinical pharmacology findings of TECARTUS (KTE-X19) in adult subjects with B-cell precursor acute lymphoblastic leukemia (ALL):

- Following infusion, KTE-X19 exhibited an initial rapid expansion phase followed by a bi-phasic decline. Within the anti-CD19 CAR T dose range of 0.5 x 10^6 to 2.0 x 10^6 anti-CD19 CAR T cells/kg, there is no clear dose-response for KTE-X19 exposure (Cmax and $AUC_{0\text{-}28d}$). Median expansion (Cmax and $AUC_{0\text{-}28d}$) of KTE-X19 was highest in subjects treated at the 1.0 x 10^6 dose level with earlier intervention with corticosteroids (modified toxicity management).
- At the anti-CD19 CAR T dose level of 1x 10^6 cells/kg with modified toxicity management (earlier intervention with corticosteroids), following infusion, KTE-X19 exhibited an initial rapid expansion phase achieving maximal expansion (Cmax) around Day 15 followed by a bi-phasic decline.
- KTE-X19 was present in peripheral blood up to 18 months post-infusion in peripheral blood at the time of the data cutoff date, demonstrating long term persistence of KTE-X19.

- Multivariate analysis indicated that lower blast percentage in bone marrow at screening and higher (b) (4) were potentially associated with higher KTE-X19 expansion.

- Subjects with overall MRD negative status during the study had substantially higher KTE-X19 expansion, compared to subjects with in overall MRD positive status. Due to the small sample size, the results need to be interpreted with caution and no definitive conclusions be made.

- Substantially higher KTE-X19 expansion was observed in responding subjects (CR + CRi), compared to non-responding (non-CR/CRi) subjects. Higher KTE-X19 expansion was positively associated with best overall response (BOR) rate.

- Higher KTE-X19 exposure was associated with Grade 2 or higher cytokine release syndrome (CRS). Median Cmax and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects with Grade 2 or higher CRS were 7.9- and 5.8-fold higher, respectively, compared to subjects with Grade 1 or no CRS.

- Higher KTE-X19 exposure was associated with Grade 2 or higher neurological events. Median of Cmax and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects with Grade 2 or higher neurological events were 6.0- and 3.0-fold higher, respectively, compared to subjects with Grade 1 or no neurological events.

- Tocilizumab and corticosteroids were used in the management of CRS and neurologic events, respectively, after treatment with KTE-X19. Higher KTE-X19 expansion (Cmax and $AUC_{0\text{-}28d}$) was observed in subjects administered tocilizumab and/or corticosteroids compared to subjects who did not take tocilizumab or corticosteroids. KTE-X19 continued to expand in subjects who received tocilizumab and corticosteroids after infusion of KTE-X19.

- Substantially elevated levels were reported in subjects who developed severe (Grade 3 or higher) CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following serum biomarkers: ferritin, granzyme B, IFN-γ, IL-2Rα, IL-6, IL-8, IL-10, IL-15, TNF-α, and GM-CSF.

- Substantially elevated levels were reported in subjects who developed severe (Grade 3 or higher) neurological events compared to subjects with Grade 2, Grade 1 or no neurological events for the following serum biomarkers: IL-1RA and IL-6.

- KTE-X19 induced B-cell aplasia in majority of the treated subjects. At 12 months post KTE-X19 infusion, the B-cell levels recovered in 100% of evaluable subjects.

- Based on results of a confirmatory cell-based assay, five subjects treated with KTE-X19 had positive results against single chain variable region fragment (scFv) in CAR at time points no earlier than 3 months after infusion. There is no evidence that the kinetics of initial expansion and persistence of KTE-X19 was altered in these subjects.

- There was no reported presence of replication-competent retrovirus (RCR) in the blood of KTE-X19 treated subjects.