

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

BLA	125643/0
Product	Axicabtagene Ciloleucel, KTE-C19, YESCARTA™
Sponsor	Kite Pharma, Inc.
Indication	Treatment of adult patients with relapsed or refractory large B-cell of the following types after two or more lines of systemic therapy: diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from follicular lymphoma
Date Received	March 31, 2017
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1 EXECUTIVE SUMMARY

Kite Pharma Inc. seeks approval of its KTE-C19 (axicabatagene ciloleucel, anti-CD19 CAR T cells, YESCARTA™) for the treatment of adult patients with relapsed or refractory large B-cell lymphoma of the following types after two or more lines of systemic therapy: diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from follicular lymphoma. KTE-C19 comprises autologous T cells transduced with retroviral vector containing an anti-CD19 chimeric antigen receptor (CAR). KTE-C19 is produced from leukapheresis material obtained from individual patients, and therefore the product is unique to each patient. The proposed KTE-C19 dosing regimen is a single target dose of 2×10^6 cells/kg body weight, with a maximum of 2×10^8 anti-CD19 CAR T cells. KTE-C19 is to be administered via intravenous (IV) infusion.

The clinical pharmacology section of this biologics license application (BLA) is supported by one Phase1/2 clinical study that evaluated the safety, efficacy, pharmacokinetic (PK) and pharmacodynamics (PD) of KTE-C19 in subjects with relapsed/refractory non-Hodgkin lymphoma (NHL).

The proposed dosing regimen of KTE-C19 administered by intravenous (IV) infusion has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable. From clinical pharmacology standpoint, the BLA is acceptable to support approval.

2 INTRODUCTION

KTE-C19 is an autologous chimeric antigen receptor (CAR) T-cell therapy that targets CD19. CD19 is a 95 kilodalton (kD) transmembrane protein selectively expressed in both normal and malignant B cells. KTE-C19 is produced from leukapheresis material obtained from the individual patient, and is, therefore, a product that is unique to each patient.

The CAR construct used for KTE-C19 comprises the following domains: 1) an anti-human CD19 single-chain variable region fragment (scFv); 2) the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte co-stimulatory receptor that plays an important role in optimizing T cell survival and function; and 3) the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor complex.

Following CAR engagement with CD19+ target cells, the CD3ζ domain activates the downstream signaling cascade that leads to T cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. The intracellular signaling domain of CD28 provides a

co-stimulatory signal that works in concert with the primary CD3 ζ signal to augment Tcell-function, including interleukin-2 (IL-2) production. In addition, activated T cells secrete cytokines and other molecules that can recruit and activate additional anti-tumor immune cells.

KTE-C19 is to be administered by intravenous infusion at a single target dose of 2×10^6 CAR T cells/kg body weight, with a maximum of 2×10^8 CAR T cells.

This application is supported by two human clinical studies:

- a pivotal Phase 1/2 study (Study No. KTE-C19-101, ZUMA-1) evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin Lymphoma (NHL)
- a supportive study (Study No.: (b) (4)) to assess the safety and feasibility of administering CAR T cells to patients with B-cell lymphoma.

(b) (4) . Based on the response and safety observations in study (b) (4) , and the need to achieve adequate lymphodepletion and therapeutic levels of KTE-C19 without intolerable toxicity, the ZUMA-1 study used a regimen of cyclophosphamide 500 mg/m² dose and fludarabine 30 mg/m² given concurrently for 3 days and a target KTE-C19 dose of 2×10^6 anti-CD19 CAR T cells/kg.

During the conduct of Study (b) (4) , changes to anti-CD19 CAR T-cell manufacturing were made to streamline and optimize process. Only 13 subjects have disease and treatment characteristics similar to those of subjects in Study ZUMA-1. The anti-CD19 CAR T cells blood levels were not measured using the validated method. Therefore, the supportive study is not included in this review.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

- Following infusion of KTE-C19 in patients with relapsed or refractory large B-cell lymphoma, KTE-C19 exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of KTE-C19 occurred within the first 7-14 days after KTE-C19 infusion.
- After infusion, the median values of C_{max} and AUC_(0-28d) of KTE-C19 in responders [complete response (CR) and partial response (PR)] were about 2-fold of C_{max} and AUC_(0-28d) in non-responders.

- Subjects with Grade 3 or higher neurologic events had significantly higher KTE-C19 expansion (C_{max} and $AUC_{(0-28d)}$) compared to subjects with Grade 2 or lower neurologic events.
- Compared to subjects with Grade 2 or lower neurologic events, subjects with Grade 3 or higher cytokine release syndrome (CRS) had higher KTE-C19 $AUC_{(0-28d)}$, but not for peak levels of KTE-C19. The difference in $AUC_{(0-28d)}$ was not statistically significant.
- Age (range: 23 – 76 years old) and gender had no significant impact on $AUC_{(0-28d)}$ and C_{max} of KTE-C19.
- Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with KTE-C19. KTE-C19 continued expansion in subjects who received tocilizumab and corticosteroids after infusion of KTE-C19.
- After KTE-C19 infusion, peak levels and $AUC_{(0-28d)}$ of a number of biomarkers were significantly higher in subjects with Grade 3 or higher neurologic events than subjects with Grade 2 or lower neurologic events. These biomarkers include IL-15, IL-6, IL-2R α , IL-8, IL-10, IFN- γ , TNF- α , IP-10, IL-2, ferritin, and IL-1RA.
- Significantly elevated peak levels and $AUC_{(0-28d)}$ were reported in subjects developed Grade 3 or higher CRS compared to subjects with Grade 2 or lower CRS for following biomarkers: IL-15, IL-6, IL-2R α , IL-10, IFN- γ , TNF- α , Granzyme B, IP-10, and IL-1RA.
- KTE-C19 induced B-cell aplasia in majority of the treated subjects. And KTE-C19 induced B-cell aplasia lasted for a period of time.
- There was no reported presence of replication-competent retrovirus (RCR) in the blood of treated subjects.

4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125643 and finds it acceptable pending the following revisions shown below.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

YESCARTA a CD19-directed genetically modified autologous T cells ~~immunotherapy~~, bind to CD19 expressing cancer cells and normal B cells. Studies demonstrate 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

In study 1, after YESCARTA infusion, pharmacodynamic responses were evaluated over a 4 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 sIL2R α were analyzed. Peak elevation was observed within the first 14 days after infusion and levels generally returned to baseline within 28 days.

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

12.3. Pharmacokinetics

Following infusion of YESCARTA in patients with relapsed or refractory large B-cell lymphoma, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after YESCARTA infusion.

Age (range: 23 – 76 years old) and gender had no significant impact on AUC_(0-28d) and C_{max} of YESCARTA.

The number of anti-CD19 CAR T cells in blood was positively associated with objective response (CR or PR). **The median** Anti-CD19 CAR T-cell C_{max} levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/ μ L vs ~~41.4~~ **21.2** cells/ μ L). Median AUC Day 0-28 in responding patients (n=73) were 251% higher of the corresponding level in nonresponders (n=23) (557.1 ~~days*cells/ μ L~~ vs. ~~403.3~~ **222.0** days*cells/ μ L).

Some patients required tocilizumab and corticosteroids for management of cytokine release syndrome (CRS) and neurologic toxicities. Patients treated with tocilizumab (n=44) had 262%

and 232% higher YESCARTA $AUC_{(0-28d)}$ and C_{max} respectively, as compared to patients who did not receive tocilizumab (n=57). Similarly, patients that received corticosteroids (n=26) had 217% and 155% higher $AUC_{(0-28d)}$ and C_{max} compared to patients who did not receive corticosteroids (n=75).

Hepatic and renal impairment studies of YESCARTA were not conducted.

5 RECOMMENDATIONS

The clinical pharmacology information in this BLA 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 4 for detailed Labeling Recommendations.

6 APPENDIX - INDIVIDUAL STUDY

6.1 Study #1

6.1.1 Study Design

Study Title: A Phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin Lymphoma (NHL) (Study No. KTE-C19-101, ZUMA-1)

Objectives

Primary Objectives

The primary objective of the Phase 1 portion of the study was to evaluate the safety of KTE-C19 regimens.

The primary objective of the Phase 2 portion of the study was to evaluate the efficacy of KTE-C19 as measured by objective response rate (ORR) in subjects with refractory aggressive non-Hodgkin Lymphoma (NHL); namely, diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL).

Secondary Objectives

The secondary objectives of Phase 2 portion of the study included assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints.

Study Design

This is an ongoing Phase 1/2 multi-center, open-label study that evaluates the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL. The study consists of Phase 1 and Phase 2 portions. In Phase 1, the safety of various conditioning chemotherapy and KTE-C19 was tested in 7 subjects with DLBCL, PMBCL, or TFL. In Phase 2, to ensure homogeneity of population within each cohort, subjects with refractory DLBCL were enrolled in Cohort 1, and subjects with refractory PMBCL or refractory TFL were included in Cohort 2. A total of 101 subjects (77 in Cohort 1 and 24 in Cohort 2) were treated in Phase 2. The demographics of the subjects are shown in Table 1. The actual dosing of KTE-C19 were 1.1×10^6 cell/kg to 2×10^6 cells/kg and 2×10^6 cells/kg for Phase 1 and Phase 2, respectively. The efficacy evaluation by independent review committee (IRC) was conducted for Phase 2 subjects only.

A third cohort in Phase 2 (Cohort 3) is examining the impact of pre-emptive management for safety in subjects with relapsed/refractory aggressive NHL who are ineligible for ASCT. This report is focused on results from Phase 1 and Phase 2, and Cohort 1 and 2.

As shown in Figure 1, enrolled subjects underwent leukapheresis to obtain peripheral blood mononuclear cells (PBMCs) for the production of KTE-C19 (anti-CD19 CAR T cells). Five days prior to hospitalization, subjects were treated with conditioning chemotherapy to prepare for KTE-C19 treatment: 500 mg/m² cyclophosphamide and 30 mg/m² fludarabine for 3 days. On Day 0, subjects received a single infusion of KTE-C19.

Table 1 Demographics Profile of Subjects (ZUMA-1, Phase 1 & Phase 2)

	Phase 1 (N = 7)	Cohort 1 (N = 77)	Phase 2 Cohort 2 (N = 24)	Total (N = 101)
Age (years)				
n	7	77	24	101
Mean (SD)	52.4 (17.5)	57.4 (10.6)	53.0 (15.5)	56.3 (12.0)
Median	59.0	58.0	57.0	58.0
Min, Max	29, 69	25, 76	23, 76	23, 76
Age Category n(%)				
<65 Years	4 (57)	60 (78)	17 (71)	77 (76)
>=65 Years	3 (43)	17 (22)	7 (29)	24 (24)
Sex n(%)				
Male	5 (71)	50 (65)	18 (75)	68 (67)
Female	2 (29)	27 (35)	6 (25)	33 (33)
Ethnicity n(%)				
Hispanic or Latino	1 (14)	16 (21)	2 (8)	18 (18)
Not Hispanic or Latino	6 (86)	61 (79)	22 (92)	83 (82)
Race n(%)				
Asian	0 (0)	1 (1)	3 (13)	4 (4)
Black or African American	1 (14)	3 (4)	1 (4)	4 (4)
White	6 (86)	71 (92)	19 (79)	90 (89)
Others	0 (0)	2 (3)	1 (4)	3 (3)
Country n(%)				
United States	7 (100)	77 (100)	23 (96)	100 (99)
Israel	0 (0)	0 (0)	1 (4)	1 (1)

Note: Percentages are based on number of subjects treated.

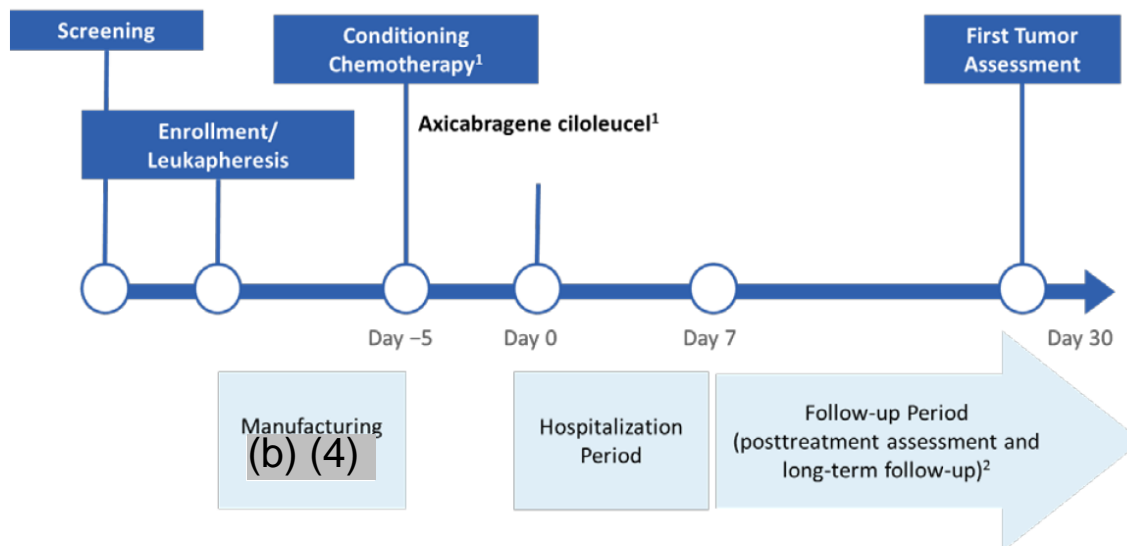
Source: Applicants Table10 in section 5.3.5.1. KTE-C19-101: Clinical Study Report, page 77

For pharmacokinetic analysis, blood samples were collected approximately 5 days prior to infusion (Day -5) to obtain baseline levels, and at 7, 14, 28 days, 3, 6, 9, 12, 15, 18, and 24 months post-infusion.

Blood levels of KTE-C19 were monitored by a validated (b) (4) assay, which is specifically designed for measuring (b) (4)

Blood samples were also obtained for pharmacodynamics biomarker analysis at the following time points: baseline (around 5 days prior to infusion, Day -5), and at 1, 3, 5, 7, 14, and 28 days post-infusion.

Figure 1 Study Process of ZUMA-1



¹ Axicabtagene ciloleucel treatment consists of conditioning chemotherapy of 500 mg/m² cyclophosphamide and 30 mg/m² fludarabine on Day -5, Day -4, Day -3 followed by a target of 2×10^6 ($\pm 20\%$) CAR T cells/kg (minimum 1×10^6 CAR T cells/kg) on Day 0.

² Long-term follow-up for disease status and survival continued every 3 months through Month 18, then every 6 months through 5 years, and then annually for a maximum of 15 years.

Source: Applicants Figure 3 in section 5.3.5.1. KTE-C19-101: Clinical Study Report, page 27

A panel of 44 homeostatic, inflammatory, and immune modulating cytokines, chemokines, and immune effector-related biomarkers were measured for pharmacodynamics assessment. Levels of following 13 key homeostatic, pro-inflammatory and immune modulating cytokines, chemokines, and immune effector analytes were evaluated with validated immunoassay methods:

- Homeostatic/proliferative: IL-15
- Inflammatory/immune modulating: tumor necrosis factor-alpha (TNF- α), IL-10, IL-13, IL-
- 12p40, IL-12p70, IL-6, CRP, interferon-gamma (IFN- γ), IL-1ra, and IL-2R α
- Chemokine: IL-8
- Immune effector: granzyme B

6.1.2 Results

6.1.2.1 Pharmacokinetics

General Pharmacokinetic Characteristics for All Treated Subjects

In ZUMA-1, a total of 107 subjects received KTE-C19 treatment and pharmacokinetic profiles were obtained for 101 subjects.

In general, the pharmacokinetic profile of KTE-C19 consists of a rapid exponential increase followed by a rapid decline and then a gradual decrease. Peak levels of KTE-C19 occurred within the first 7-14 days after KTE-C19 infusion. The median peak level of KTE-C19 in the blood (C_{max}) were 41.9 cells/μL (range: 0.8 - 1513.7 cells/μL). The median area under the blood concentration vs. time curve from Day 0 to Day 28 (AUC_(0-28d)) was 462.3 days*cells/μL (range 5.1 – 14329.3 days*cells/μL). At 1 month after KTE-C19 infusion, the median blood level of KTE-C19 was 2.1 cells/μL (range: 0 – 167.4 cells/μL), and by 3 months, levels of KTE-C19 decreased to a median of 0.4 cells/μL (range: 0 – 15.8 cells/μL).

Pharmacokinetics in Special Population or Subgroups

Elderly

In ZUMA-1, 25% of the total subjects were ≥ 65 years of age. The median (range) of AUC_(0-28d) were 564.2 days*cells/mL (16.8 – 6158.4 days*cells/mL) and 448.4 days*cells/mL (5.1 – 14329.3 days*cells/mL) for elderly subjects (≥ 65 years of age) and less than 65 years old subjects, respectively. The median (range) of KTE-C19 peak levels were 44.3 cells/mL (1.2 – 404.0 cells/mL) vs. 35.3 cells/mL (0.8 – 1513.7 cells/mL) for subjects ≥ 65 years and < 65 years respectively. The median values of the time to reach peak levels of KTE-C19 (T_{max}) were 8.0 days for both subject groups. No statistically significant difference of pharmacokinetic parameters was found between elderly subjects and overall study population. This may due to high variability of PK parameters and small sample size.

Pediatric Patients

The safety and efficacy of KTE-C19 in pediatric subjects has not been studied in ZUMA-1.

Gender

In ZUMA-1, 73 subjects (68%) were male and 34 (32%) were female. The median (range) AUC_(0-28d) of KTE-C19 were 469.3 days*cells/mL (14.4 – 11506.6 days*cells/mL) and 404.5 days*cells/mL (5.1 – 14329.3 days*cells/mL) for male and female subjects respectively. The median (range) C_{max} of KTE-C19 were 43.2 cells/mL (0.8 – 1513.7 cells/mL) and 31.5 cells/mL (1.5 – 1226.4 cells/mL) for male and female respectively. The median values of the time to reach peak levels of KTE-C19 (T_{max}) were 8.0 days for both groups. Due to high

variability of PK parameters and small sample size, no statistically significant impact of gender on PK parameters ($AUC_{(0-28d)}$ and C_{max}) was found.

Race

The populations studied in ZUMA-1 were primarily Caucasian, non-Hispanic subjects. Therefore, comparisons across race or ethnicity were not possible.

Renal Impairment

The effect of renal impairment was not assessed.

Hepatic Impairment

The effect of hepatic impairment was not assessed.

Impacts of Tocilizumab and Corticosteroids on KTE-C19 Pharmacokinetics

Tocilizumab and corticosteroids were used in the management of cytokine release syndrome (CRS) and neurologic events in the study ZUMA-1. Subjects treated with tocilizumab (n=44) had 262% and 232% higher of median KTE-C19 $AUC_{(0-28d)}$ and C_{max} respectively, as compared to subjects who did not receive tocilizumab (n=57) (Table 2). Similarly, subjects that received corticosteroids (n=26) had 217% and 155% higher median $AUC_{(0-28d)}$ and C_{max} compared to patients who did not receive corticosteroids (n=75) (Table 3).

Table 2 Analysis of Peak and $AUC_{(0-28d)}$ of KTE-C19 (Anti-CD19 CAR T Cells) by Tocilizumab Taken (ZUMA-1, Phase 1 & Phase 2)

	Tocilizumab Taken Post KTE-C19 Infusion up to Hospital Charge	
	Yes (N=44)	No (N=57)
Area Under Curve (From Day 0 to Day 28)		
Mean	1299.5	728.1
Median (Q1, Q3)	784.3 (383.1, 1142.3)	299.4 (108.2, 566.3)
Min, Max	14.4, 11506.6	16.8, 14329.3
Peak		
Mean	128.1	61.4
Median (Q1, Q3)	61.1 (34.0, 108.1)	26.4 (10.0, 62.5)
Min, Max	0.8, 1513.7	1.2, 1226.4
Time to Peak		
Median (Q1, Q3)	8.0 (8.0, 13.5)	8.0 (8.0, 15.0)
Min, Max	7.0, 28.0	7.0, 78.0

Table 3. Analysis of Peak and AUC_(0-28d) of KTE-C19 (Anti-CD19 CAR T Cells) by Corticosteroids Taken (ZUMA-1, Phase 1 & Phase 2)

	Steroids Taken Post KTE-C19 Infusion up to Hospital Charge	
	Yes (N=26)	No (N=75)
Area Under Curve (From Day 0 to Day 28)		
Mean	1361.6	843.7
Median (Q1, Q3)	797.3 (323.7, 1145.7)	366.7 (133.8, 844.7)
Min, Max	14.4, 11506.6	16.8, 14329.3
Peak		
Mean	135.5	74.9
Median (Q1, Q3)	49.7 (32.1, 96.1)	32.0 (12.0, 74.7)
Min, Max	0.8, 1513.7	1.2, 1226.4
Time to Peak		
Median (Q1, Q3)	8.0 (8.0, 13.25)	8.0 (8.0, 15.0)
Min, Max	7.0, 16.0	7.0, 78.0

Conditioning Chemotherapy and KTE-C19 Pharmacokinetics

Conditioning chemotherapy significantly increased the levels of IL-15 from baseline of 3.2 pg/mL (range: 1.4 – 25.7 pg/mL) to 34.5 pg/mL (range: 6.5 – 205.2 pg/mL) on Day 0 prior to KTE-C19 infusion. However, statistical analysis did not show associations between levels of serum IL-15 at Day 0 and pharmacokinetic profiles of KTE-C19.

Product Characteristics and KTE-C19 Pharmacokinetics

KTE-C19 an autologous chimeric antigen receptor (CAR) T-cell therapy and the product characteristics may affect KTE-C19 proliferation after infusion. Exploratory analysis was conducted to evaluate the impact of pre-infusion product characteristics on KTE-C19 expansion and clinical outcome in ZUMA-1 Phase 2 subjects. Following product characteristics were evaluated: (b) (4)

As shown in Table 4, post-infusion KTE-C19 levels were found to be positively statistically significantly associated with total number of (b) (4)

IFN- γ showed a positive and negative trend with post-infusion levels of KTE-C19 respectively, but the associations were not statistically significant.

There were no associations identified between post-infusion KTE-C19 blood levels and following product characteristics: (b) (4)

Table 4. Associations of Post-infusion Blood KTE-C19 (Anti-CD19 CAR T Cells) Levels with Product Characteristics or Treatment-related Covariates (ZUMA-1, Phase 2)

Product Character	Number of Evaluable Subjects	Regression coefficient (95% CI)	p-value
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(b) (4)

Source: Applicants Table 7 in section 5.3.4.2. ZUMA-1 PK-PD Report, page 31

There is no relationship between product characteristics and Day 0 cytokines in serum with subjects' objective response. The clinical relevance between product characteristics and KTE-C19 treatment efficacy cannot be identified.

Tumor Burden and KTE-C19 Pharmacokinetics

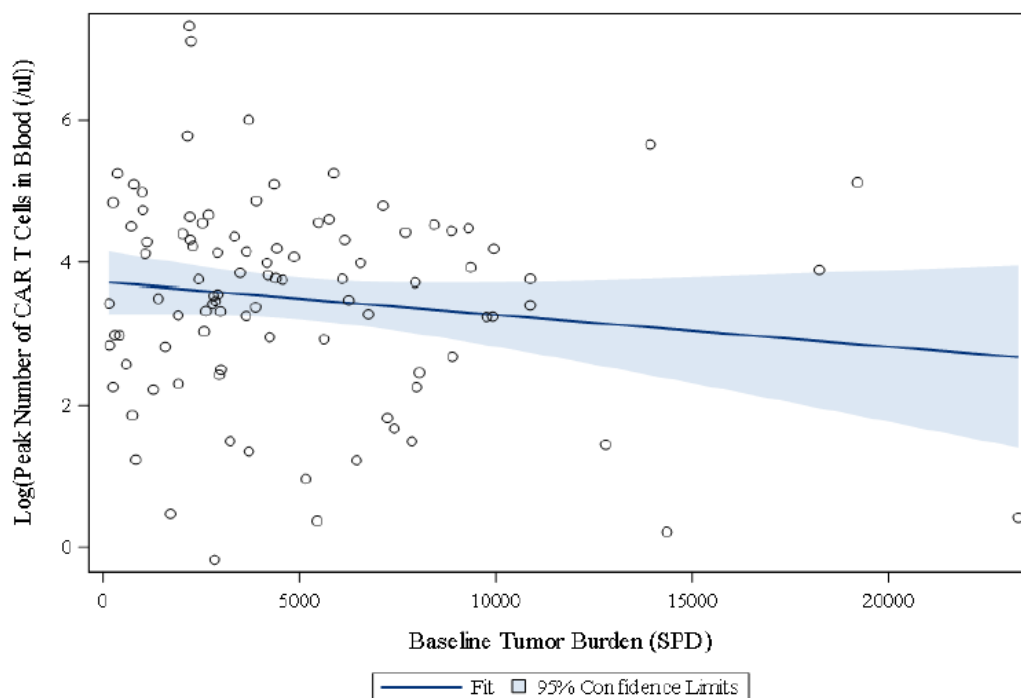
After infusion, KTE-C19 engages with CD19+ target cells. The interaction between KTE-C19 and the CD19 expressing malignant B cells may impact KTE-C19 pharmacokinetic profile. The association between tumor burden (TB) at baseline and KTE-C19 pharmacokinetics was assessed. Baseline tumor burden was computed by adding the sum of the longest diameter and the perpendicular diameter of each target lesion assessment during screening. No association between baseline tumor burden and KTE-C19 expansion can be identified.

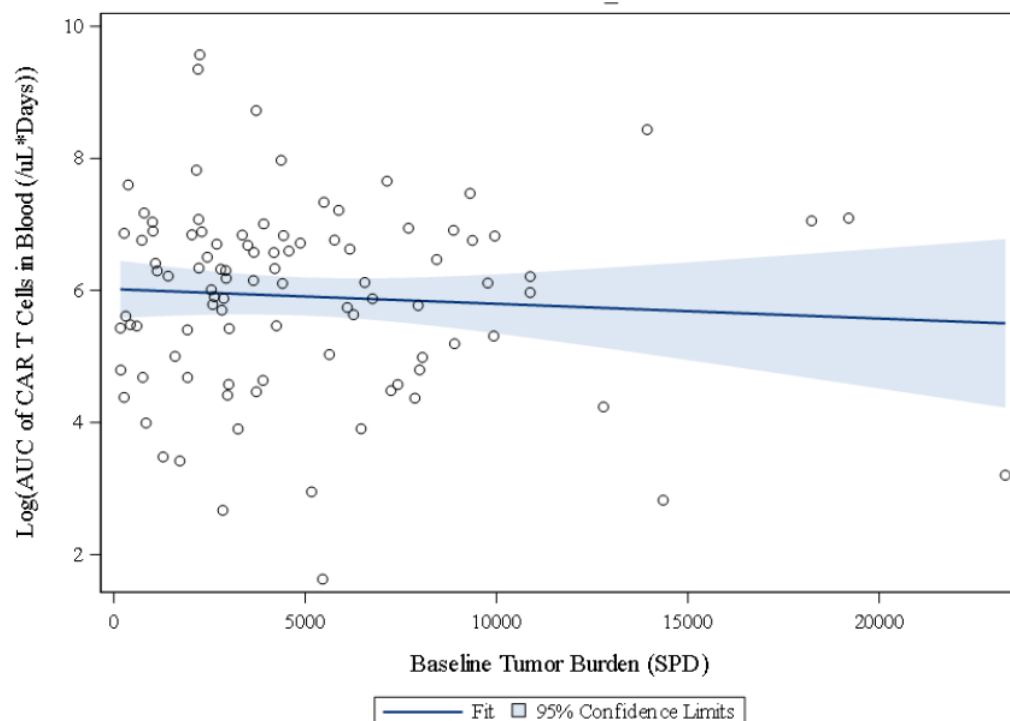
Table 5 shows the quartile analysis of tumor burden relative to KTE-C19 peak levels, AUC_(0-28d) and time to peak in blood.

Table 5. Summary of KTE-C19 (Anti-CD19 CAR T Cells) Expansion by Peak, AUC_(0-28d) and Time to Peak (median, Q1 and Q3) by Quartiles of Baseline Tumor Burden

Quartiles of Baseline Tumor Burden	Tumor Burden at Baseline [mm ²] (median Q1, Q2)	Peak Number of anti-CD19 CAR T cells in Blood [cells/uL] (median Q1, Q2)	Time to Peak [days] (median Q1, Q2)	AUC ₀₋₂₈ of Number of anti-CD19 CAR T cells in Blood [cells/uL·Days] (median Q1, Q2)
≤ Q1	1015 (431, 1724)	31.0 (13.2, 114.0)	8 (8, 8)	273.3 (120.8, 959.4)
Q1 < - ≤ Median	2871 (2584, 3245)	35.3 (26.2, 74.8)	8 (8, 15)	484.6 (299.4, 799.7)
Median < - ≤ Q3	5167 (4371, 6100)	45.6 (26.7, 95.4)	8 (8, 15)	562.0 (236.4, 926.3)
> Q3	9371 (7991, 12795)	30.3 (6.2, 83.0)	15 (8, 15)	391.0 (97.0, 1003.9)

Source: Applicants Table 2 in section 1.12.4 Response to Clinical Pharmacology IR – 02Aug2017, page 2

Figure 2 Linear Regression of KTE-C19 (Anti-CD19 CAR T Cells) Expansion (Peak levels and AUC_(0-28d)) and Baseline Tumor Burden



Source: Applicants Figure 1 & 2 in section 1.12.4 Response to Clinical Pharmacology IR – 02Aug2017, page 3-4

6.1.2.2 Exposure-Response Relationship

Exposure-Response for Efficacy

The relationship between KTE-C19 exposure and efficacy was based on results of IRC best overall response (BOR) assessment which was performed for ZUMA-1 Phase 2 subjects only. Among subjects in the Phase 2 portion of ZUMA-1, the systemic exposure of KTE-C19 was positively associated with subjects' objective responses [complete response (CR) or partial response (PR) and non-response (NR)]. The median KTE-C19 C_{max} levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/μL vs 21.2 cells/μL). Median AUC Day 0-28 in responding patients (n=73) were 251% higher of the corresponding level in nonresponders (n=23) (557.1 days*cells/μL vs. 222.0 days*cells/μL). The median T_{max} in both responding and non-responding patients groups occurred on day 8. A summary of comparison of KTE-C19 pharmacokinetic parameters between responding and non-responding patients is provided in Table 6 below.

Table 6. Comparison of KTE-C19 (Anti-CD19 CAR T Cells) Pharmacokinetic Parameters between Responding and Non-Responding Patients

Parameters (Unit)	Unit	Responding Patients N=73	Non-Responding Patients N=23
C _{max} [median, (min, max)]	Cells/ μ L	43.6 (0.8, 1513.7)	21.2 (1.2, 167.4)
T _{max} [median, (min, max)]	Days	8.0 (7.0, 29.0)	8.0 (7.00 – 78.0)
AUC _(0-28d) [median, (min, max)]	Days*cells/ μ L	557.1 (14.4, 14329.3)	222.0 (16.8, 2112.8)

Note: The analysis is based on the results of IRC Best Response evaluation which was conducted in Phase 2 subjects. Five subjects were excluded from analysis due to that PK samples were not collected with sufficient time points to characterize PK profiles from day 0-28.

Exposure-Response for Safety

Exposure and Cytokine Release Syndrome (CRS)

Subjects with Grade 3 or higher CRS had higher cumulative levels of KTE-C19 over the first 4 weeks than subjects with Grade 2 or lower CRS (median AUC_(0-28d): 601.5 days*cells/ μ L vs. 453.4 days*cells/ μ L). Both groups of subjects had the median T_{max} on Day 8.0. The differences in AUC_(0-28d) and C_{max} between the two groups were not statistically significant. No remarkable difference was observed in median peak levels of KTE-C19 between subjects with Grade 3 or higher CRS and subjects with Grade 2 or lower CRS: 41.9 cells/ μ L vs. 38.7 cells/ μ L (Table 7).

Table 7. Summary of KTE-C19 (Anti-CD19 CAR T Cells) Expansion and Cytokine Release Syndrome

Number of CAR T Cells median(range)	Cytokine Release Syndrome Subgroupss		
	With Grade 3 or higher (N = 13)	Grade 2 or lower (N = 88)	P-value
AUC	601.5 (14.4, 11506.6)	453.4 (5.1, 14329.3)	0.3379
Peak	41.9 (0.8, 1513.7)	38.7 (1.2, 1226.4)	0.2850

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Peak is defined as the maximum number of CAR T measured post infusion.
Area under curve (AUC) is defined as the area under curve in a plot of number of CAR T cells against scheduled visit from Day 0 to Day 28.
P-value is calculated by Wilcoxon rank sum test, a rank-based nonparametric test for 2 groups comparison.
Subgroup of worst grade 2 or lower includes the subjects who did not have the event onset.

Source: Applicants Table 14.9.4.2 in section 5.3.4.2. ZUMA-1 PK-PD Report, page 60

Exposure and Neurologic Events

Subjects with severe neurologic events had significantly higher exposure of KTE-C19 than subjects with no or less severe neurologic events. Median peak KTE-C19 levels in blood were significantly increased by 2-fold in subjects with Grade 3 or higher neurologic events relative to levels in subjects with Grade 2 or lower neurologic events (63.5 cells/ μ L vs. 30.9 cells/ μ L; Wilcoxon rank-sum test $P=0.0129$). Similar trend was found in $AUC_{(0-28d)}$ of KTE-C19 over the first 4 weeks: median $AUC_{(0-28d)}$: 826.3 days*cells/ μ L vs. 321.2 days*cells/ μ L (subjects with Grade 3 or higher neurologic events vs. subjects with Grade 2 or lower neurologic events) (Table 8). Both groups of subjects had the median T_{max} on Day 8.0.

Table 8. Summary of KTE-C19 (Anti-CD19 CAR T Cells) Expansion and Neurologic Events

Number of CAR T Cells median(range)	Neurologic Events Subgroupss		
	With Grade 3 or higher (N = 28)	Grade 2 or lower (N = 73)	P-value
AUC	826.3 (5.1, 6158.4)	321.2 (16.8, 14329.3)	0.0028
Peak	63.5 (0.8, 404.0)	30.9 (1.2, 1513.7)	0.0129

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Peak is defined as the maximum number of CAR T measured post infusion.
Area under curve (AUC) is defined as the area under curve in a plot of number of CAR T cells against scheduled visit from Day 0 to Day 28.
P-value is calculated by Wilcoxon rank sum test, a rank-based nonparametric test for 2 groups comparison.
Subgroup of worst grade 2 or lower includes the subjects who did not have the event onset.

Source: Applicants Table 14.9.4.1 in section 5.3.4.2. ZUMA-1 PK-PD Report, page 59

6.1.2.3 Pharmacodynamics

For pharmacodynamics assessment in ZUMA-1, the sponsor measured a panel of 44 homeostatic, inflammatory, and immune modulating cytokines, chemokines, and immune

effector-related biomarkers prior to KTE-C19 and at various time points post infusion. Levels of 13 selected key homeostatic, pro-inflammatory and immune modulating cytokines, chemokines, and immune effector analytes were evaluated. Table 9 shows changes of serum levels of these 13 key biomarkers during the study.

After infusion of KTE-C19, levels of most of the 13 key biomarkers increased to peak levels within first 14 days post infusion, and then returned to baseline within 28 days (Table 9). More than 50% subjects had a ≥ 2 -fold increase at peak from baseline for following biomarkers: CRP, Granzyme B, IFN- γ , IL-1 RA, IL-2R alpha, IL-6, IL-8, IL-10, and IL-15 (Table 10).

Exploratory statistical analysis did not show correlation between cytokine exposures (peak levels and AUC_(0-28d)) and KTE-C19 expansion.

In addition, statistical analysis did not reveal correlation between cytokines levels on Day 0 and safety outcome (CRS and neurologic events).

Table 9. Summary of Levels of Pharmacodynamic Biomarkers

Cytokine	Baseline (N=90)	Day 0 (N=100)	Peak (N=101)	Week 4 (N=93)
	Median (range)			
CRP (mg/L)	28.9 (0.7, 496.0)	36.1 (0.9, 496.0)	214.2 (18.5, 496.0)	1.9 (0.0, 198.3)
Granzyme B (pg/mL)	1.0 (1.0, 59.3)	1.0 (1.0, 334.1)	22.7 (1.0, 3306.0)	1.0 (1.0, 44.1)
IFN-gamma (pg/mL)	7.5 (7.5, 81.9)	7.5 (7.5, 1876.0)	477.4 (7.5, 8209.2)	7.5 (7.5, 249.1)
IL-1 RA (pg/mL)	577.6 (224.9, 5673.4)	503.4 (98.4, 5034.6)	2314.2 (510.8, 40000.0)	461.5 (110.7, 3318.8)
IL-2 R alpha (pg/mL)	2784.4 (78.0, 33265.4)	2766.7 (78.0, 69904.8)	12133.6 (78.0, 100000.0)	2188.2 (78.0, 26643.7)
IL-6 (pg/mL)	3.7 (1.6, 150.3)	3.4 (1.6, 123.1)	83.3 (3.5, 12109.7)	3.8 (1.6, 976.0)
IL-8 (pg/mL)	12.7 (1.1, 198.3)	12.2 (1.1, 299.0)	93.6 (9.8, 2664.4)	14.3 (3.3, 1113.9)
IL-10 (pg/mL)	0.7 (0.7, 38.0)	0.7 (0.7, 42.0)	41.0 (0.7, 466.0)	0.7 (0.7, 9.2)
IL-12 P40 (pg/mL)	165.9 (5.7, 4500.0)	88.8 (5.7, 4500.0)	266.2 (25.3, 4500.0)	165.6 (5.7, 860.2)
IL-12 P70 (pg/mL)	1.2 (1.2, 1.2)	1.2 (1.2, 206.1)	1.2 (1.2, 206.1)	1.2 (1.2, 6.5)
IL-13 (pg/mL)	4.2 (4.2, 4.2)	4.2 (4.2, 4.2)	4.2 (4.2, 86.5)	4.2 (4.2, 4.2)
IL-15 (pg/mL)	3.2 (1.4, 25.7)	34.5 (6.5, 205.2)	52.9 (11.3, 226.6)	4.3 (1.4, 80.1)
TNF alpha (pg/mL)	3.7 (0.7, 33.4)	3.1 (0.7, 52.2)	7.9 (2.2, 166.9)	3.0 (0.7, 18.6)

Notes: All data are median (min. max); fold change from baseline is defined as (level of cytokine - Baseline)/Baseline; peak is defined as the maximum postbaseline level of the cytokine. Baseline: last value measured prior to conditioning chemotherapy; Day 0: value measured on KTE-C19 infusion day; Week 4: value measured within the window of Day 22 to 42, and closest to Day 28.

Source: Applicants Table 4. in section 5.3.4.2. ZUMA-1 PK-PD Report, page 16

Table 10. Number of Subjects with 2-fold or Higher Change from Baseline at Peak and Week 4

Cytokine	At Peak (N=90)	At Week 4 (N=60)
	N (%)	N (%)
CRP (mg/L)	67 (74.4)	3 (5.0)
Granzyme B (pg/mL)	79 (87.8)	16 (26.7)
IFN-gamma (pg/mL)	87 (96.7)	22 (36.7)
IL-1 RA (pg/mL)	59 (65.6)	2 (3.3)
IL-2 R alpha (pg/mL)	64 (71.1)	14 (23.3)
IL-6 (pg/mL)	78 (86.7)	30 (50.0)
IL-8 (pg/mL)	73 (81.1)	3 (5.0)
IL-10 (pg/mL)	83 (92.2)	15 (25.0)
IL-12 P40 (pg/mL)	13 (14.4)	5 (8.3)
IL-12 P70 (pg/mL)	15 (16.7)	2 (3.3)
IL-13 (pg/mL)	6 (6.7)	0 (0.0)
IL-15 (pg/mL)	88 (97.8)	17 (28.3)
TNF alpha (pg/mL)	24 (26.7)	2 (3.3)

Peak is defined as the maximum postbaseline level of the cytokine.

Fold change from baseline at Day X = (Cytokine level at Day X - Baseline value) / Baseline, where Day X is the day of the peak or Day 28.

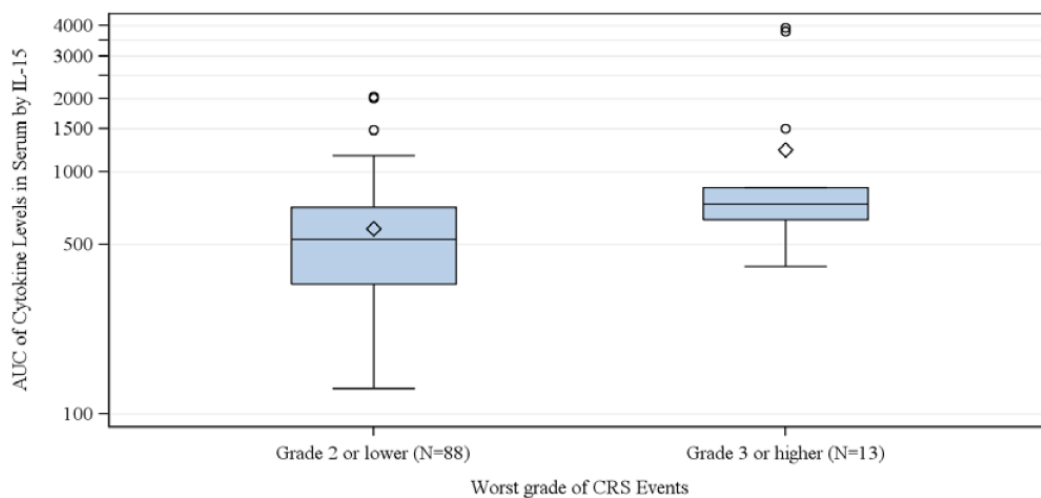
Source: Applicants Table 5. in section 5.3.4.2. ZUMA-1 PK-PD Report, page 17

Pharmacodynamic Biomarkers and Safety

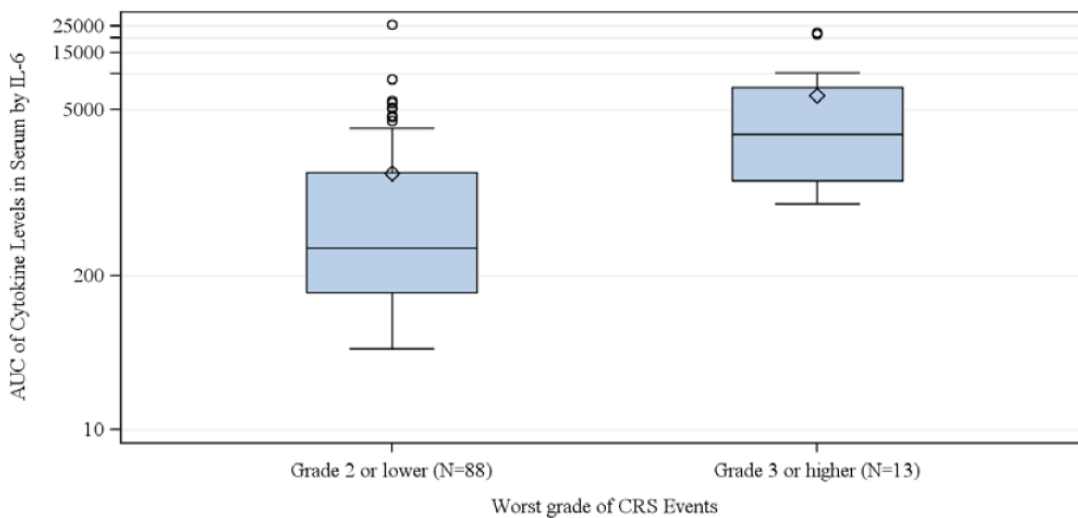
Correlative analysis was performed between pharmacodynamics biomarkers and safety in Phase 2 subjects (Table 11).

Pharmacodynamic Biomarkers and Cytokine Release Syndrome (CRS)

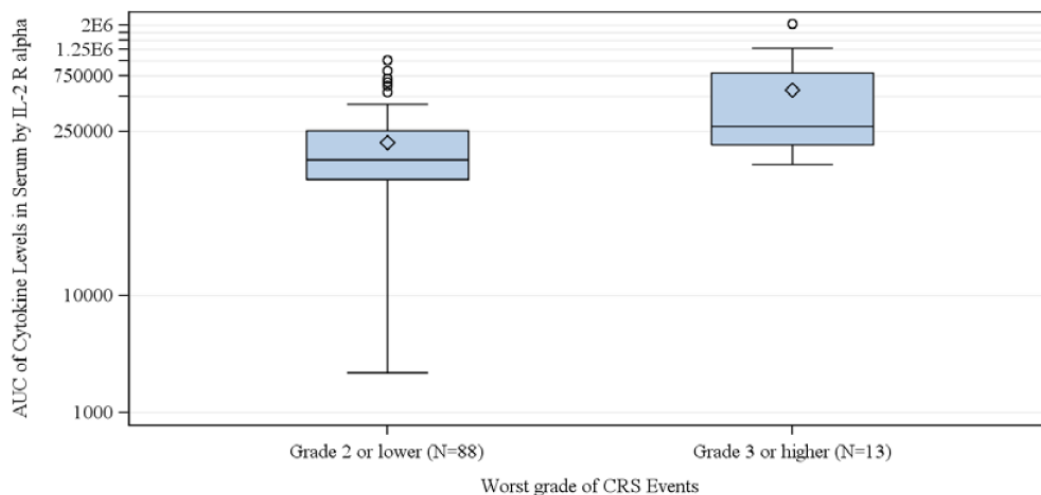
Significantly elevated peak levels and AUC_(0-28d) were reported in subjects who developed Grade 3 or higher CRS compared to subjects with Grade 2 or lower CRS for the following biomarkers: IL-15, IL-6, IL-2R α , IL-10, IFN- γ , TNF- α , Granzyme B, IP-10, and IL-1RA. Bonferroni-stepdown corrected P-values for these analytes were less than 0.05.

Figure 3. Correlation of AUC for Serum Cytokines and Grade 3 or Higher CRS Events**a. IL-15**

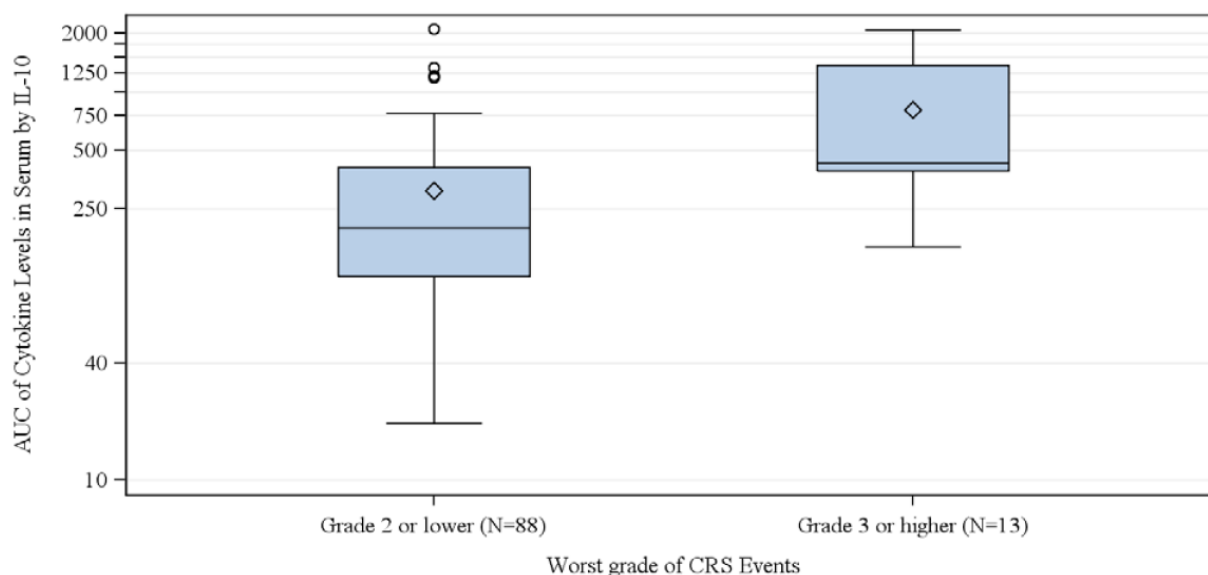
To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

b. IL-6

To apply the log scale on y-axis with zero values, all the numbers were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

c. IL-2R α 

To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

d. IL-10

To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

Source: Applicants Table 7, 8, 9, 10. in section 5.3.4.2. ZUMA-1 PK-PD Report, page 25-26

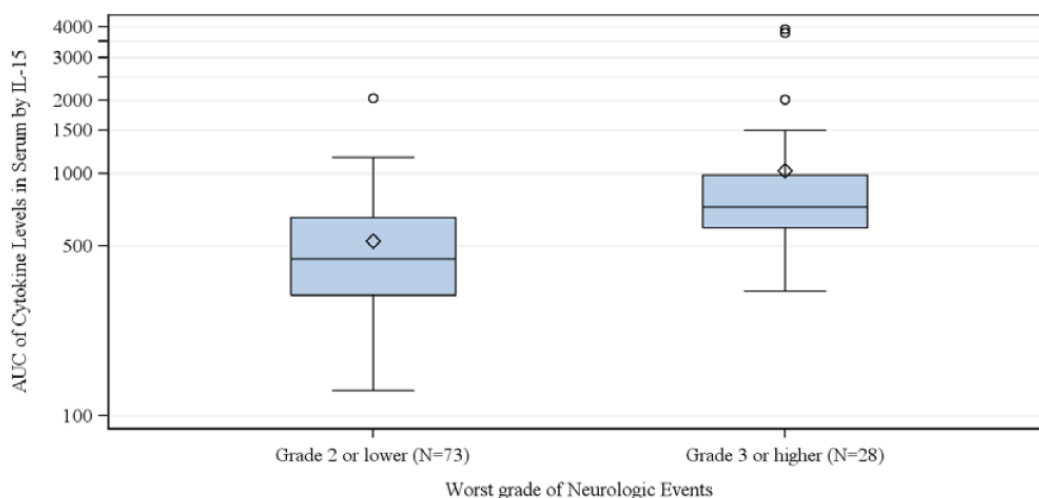
Pharmacodynamic Biomarkers and Neurologic Events

Peak levels and AUC_(0-28d) of a number of biomarkers were significantly higher in subjects with Grade 3 or higher neurologic events than subjects with Grade 2 or lower neurologic events: IL-15, IL-6, IL-2R α , IL-8, IL-10, IFN- γ , TNF- α , IP-10, and IL-1RA (all P < 0.05 by Bonferroni-

stepdown). It was noticed that peak levels and $AUC_{(0-28d)}$ of IL-2 and ferritin were associated with Grade 3 or higher neurologic events ($P < 0.05$ after multiplicity adjustment) but were not significantly associated with CRS.

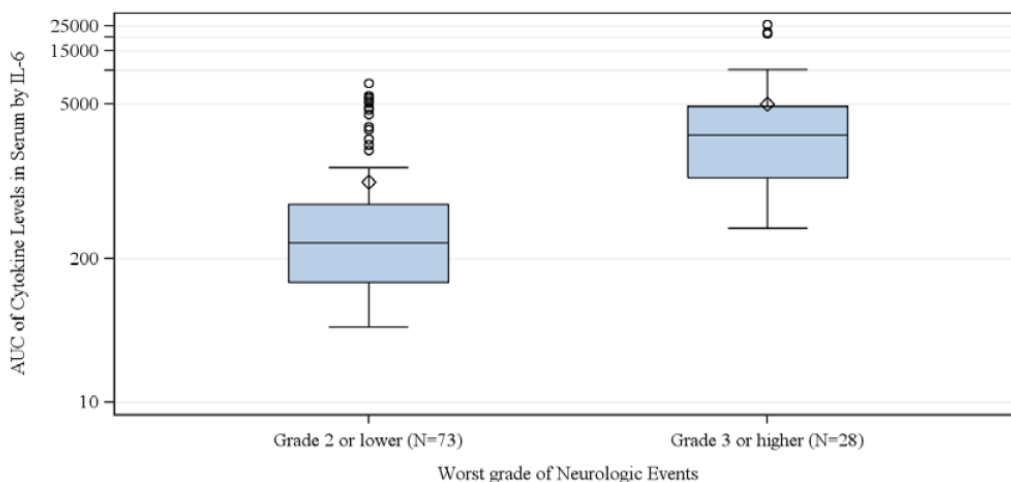
Figure 4. Correlation of AUC for Serum Cytokines and Grade 3 or Higher Neurologic Events

a. IL-15

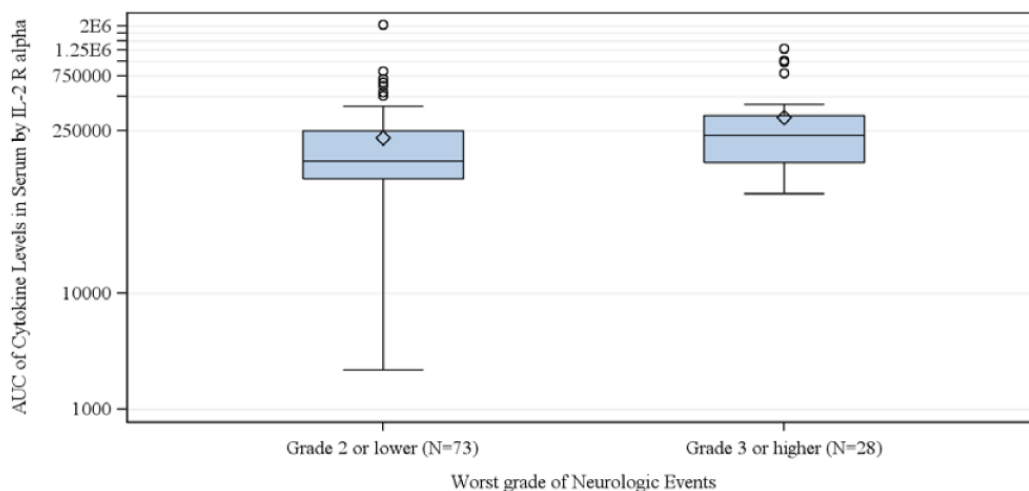


To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

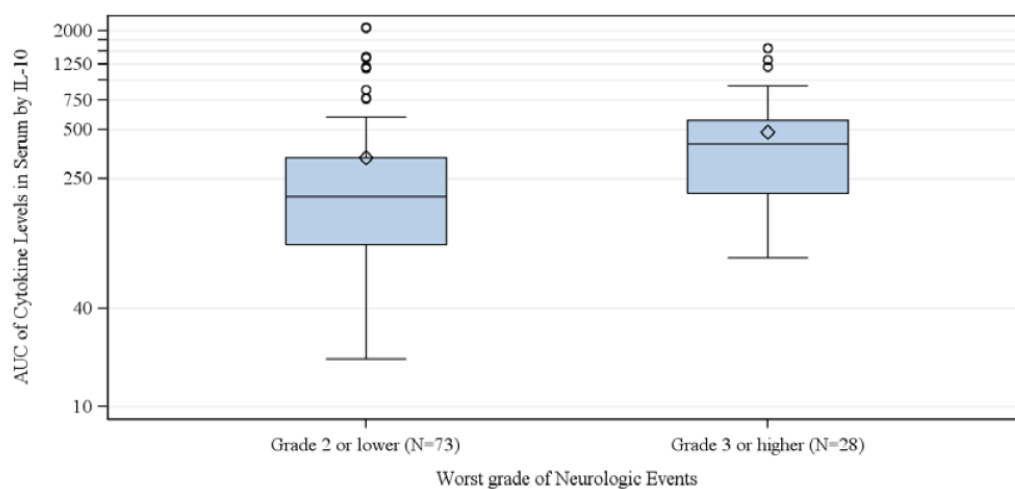
b. IL-6



To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

c. IL-2R α 

To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

d. IL-10

To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28. Diamonds represent mean values; circles represent the outliers

Source: Applicants Table 11, 12, 13, 14. in section 5.3.4.2. ZUMA-1 PK-PD Report, page 27-28

Table 11. Summary of Cytokines Peak Levels and AUC_(0-28d) in Serum with Safety Outcomes

Cytokine median(range)	Neurologic Events Subgroups			Cytokine Release Syndrome		
	With Grade 3 or higher (N = 28)	Grade 2 or lower (N = 73)	Original P-value (Adjusted p-value)	With Grade 3 or higher (N = 13)	Grade 2 or lower (N = 88)	Original P-value (Adjusted p-value)
IP-10 (pg/mL)						
Peak	2043.4 (1477.8, 40000.0)	2000.0 (434.2, 9768.7)	0.0000 (0.0004)	2401.4 (1518.4, 40000.0)	2000.0 (434.2, 40000.0)	0.0019 (0.0266)
AUC	32155.4 (13806.7, 243296.1)	25401.2 (4550.8, 81754.5)	0.0053 (0.0424)	39235.3 (17831.4, 243296.1)	27352.7 (4550.8, 81754.5)	0.0023 (0.0268)
IL-15 (pg/mL)						
Peak	70.7 (27.7, 210.6)	43.6 (11.3, 226.6)	0.0000 (0.0001)	78.6 (31.5, 210.6)	48.2 (11.3, 226.6)	0.0036 (0.0462)
AUC	725.7 (327.0, 3930.1)	445.3 (127.6, 2044.5)	0.0000 (0.0003)	737.8 (408.3, 3930.1)	524.2 (127.6, 2044.5)	0.0034 (0.0290)
IL-6 (pg/mL)						
Peak	302.5 (26.6, 12109.7)	36.1 (3.5, 1386.9)	0.0000 (0.0000)	713.9 (152.5, 5070.5)	49.4 (3.5, 12109.7)	0.0000 (0.0008)
AUC	2589.6 (373.8, 25914.4)	276.8 (47.8, 7636.8)	0.0000 (0.0000)	3099.6 (800.0, 22249.0)	338.2 (47.8, 25914.4)	0.0000 (0.0004)
IL-8 (pg/mL)						
Peak	274.6 (37.0, 2664.4)	68.3 (9.8, 750.0)	0.0000 (0.0004)	495.5 (25.9, 1260.0)	81.0 (9.8, 2664.4)	0.0082 (0.0603)
AUC	1571.3 (343.8, 21065.0)	730.8 (126.2, 5229.9)	0.0001 (0.0018)	3227.9 (415.1, 21065.0)	761.5 (126.2, 6099.8)	0.0028 (0.0282)
TNF alpha (pg/mL)						
Peak	12.0 (5.7, 166.9)	6.9 (2.2, 43.5)	0.0000 (0.0000)	15.9 (6.5, 166.9)	7.5 (2.2, 52.2)	0.0003 (0.0043)
AUC	161.8 (78.7, 1501.9)	117.9 (41.1, 613.6)	0.0006 (0.0073)	179.0 (92.0, 1501.9)	121.4 (41.1, 345.7)	0.0032 (0.0290)

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Peak is defined as the maximum postbaseline level of the cytokine.
Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28.
Original P-value is calculated by Wilcoxon rank sum test, a rank-based nonparametric test for 2 groups comparison;
Adjusted p-values are generated by a multiplicity-control procedure (Holm 's method) due to the comparisons done for each of the pre-selected cytokines in the table.
Subgroup of worst grade 2 or lower includes the subjects who did not have the event onset.

Source: Applicants Table 14.9.6.1 in section 5.3.4.2. ZUMA-1 PK-PD Report, page 268

Table 11. Summary of Cytokines Peak Levels and AUC_(0-28d) in Serum with Safety Outcomes (continued)

Cytokine median(range)	Neurologic Events Subgroups			Cytokine Release Syndrome		
	With Grade 3 or higher (N = 28)	Grade 2 or lower (N = 73)	Original P-value (Adjusted p-value)	With Grade 3 or higher (N = 13)	Grade 2 or lower (N = 88)	Original P-value (Adjusted p-value)
IFN-gamma (pg/mL)						
Peak	995.5 (97.2, 8209.2)	350.8 (7.5, 2585.1)	0.0004 (0.0043)	955.4 (249.1, 8209.2)	366.7 (7.5, 7058.9)	0.0044 (0.0462)
AUC	4257.2 (891.8, 43235.4)	1681.3 (247.5, 21598.0)	0.0003 (0.0045)	7146.3 (1688.3, 43235.4)	2052.0 (247.5, 21598.0)	0.0022 (0.0268)
Ferritin (pg/mL)						
Peak	5664150.0 (1093900.0, 25000000.0)	2128500.0 (780.0, 25000000.0)	0.0006 (0.0071)	5544900.0 (1205000.0, 25000000.0)	2788300.0 (780.0, 25000000.0)	0.0521 (0.3126)
AUC	85655252.5 (19719750.0, 339830350.0)	38925500.0 (21840.0, 537182065.0)	0.0041 (0.0368)	60444100.0 (22993300.0, 485238100.0)	41795675.0 (21840.0, 537182065.0)	0.0751 (0.3756)
VCAM-1 (pg/mL)						
Peak	1684509.8 (782485.4, 3369405.4)	1276795.4 (634769.7, 3859375.8)	0.0009 (0.0088)	2004298.3 (857636.7, 2508652.8)	1371132.8 (634769.7, 3859375.8)	0.0075 (0.0603)
AUC	33275107.8 (11787107.0, 60882299.5)	26174140.4 (12266209.9, 102187125.0)	0.0177 (0.0877)	42838448.1 (19493053.7, 62110689.0)	26319940.2 (11787107.0, 102187125.0)	0.0009 (0.0126)
IL-10 (pg/mL)						
Peak	82.7 (6.2, 466.0)	25.5 (0.7, 466.0)	0.0017 (0.0155)	124.7 (23.7, 466.0)	28.3 (0.7, 466.0)	0.0013 (0.0196)
AUC	406.0 (81.4, 1556.7)	193.5 (19.6, 2090.9)	0.0011 (0.0123)	431.7 (158.5, 2070.2)	198.3 (19.6, 2090.9)	0.0006 (0.0086)

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Peak is defined as the maximum postbaseline level of the cytokine.
Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28.
Original P-value is calculated by Wilcoxon rank sum test, a rank-based nonparametric test for 2 groups comparison;
Adjusted p-values are generated by a multiplicity-control procedure (Holm 's method) due to the comparisons done for each of the pre-selected cytokines in the table.
Subgroup of worst grade 2 or lower includes the subjects who did not have the event onset.

Table 11. Summary of Cytokines Peak Levels and AUC_(0-28d) in Serum with Safety Outcomes (continued)

Cytokine median(range)	Neurologic Events Subgroups			Cytokine Release Syndrome		
	With Grade 3 or higher (N = 28)	Grade 2 or lower (N = 73)	Original P-value (Adjusted p-value)	With Grade 3 or higher (N = 13)	Grade 2 or lower (N = 88)	Original P-value (Adjusted p-value)
IL-1 RA (pg/mL)						
Peak	3261.0 (814.6, 40000.0)	2052.8 (510.8, 14781.9)	0.0023 (0.0183)	4000.0 (1263.4, 40000.0)	2074.1 (510.8, 40000.0)	0.0058 (0.0526)
AUC	31404.7 (5589.5, 119009.9)	22546.4 (9526.5, 50263.8)	0.0006 (0.0073)	41914.5 (16950.7, 119009.9)	23284.0 (5589.5, 57548.8)	0.0004 (0.0065)
Granzyme B (pg/mL)						
Peak	41.2 (5.3, 3306.0)	17.8 (1.0, 1005.7)	0.0052 (0.0363)	55.6 (7.7, 1005.7)	19.6 (1.0, 3306.0)	0.0036 (0.0462)
AUC	189.8 (38.8, 1148.6)	135.5 (19.0, 3672.8)	0.0175 (0.0877)	332.3 (38.8, 3672.8)	147.9 (19.0, 1148.6)	0.0044 (0.0311)
IL-2 (pg/mL)						
Peak	32.0 (6.1, 113.2)	16.7 (0.9, 123.1)	0.0054 (0.0363)	29.7 (8.5, 123.1)	19.4 (0.9, 113.2)	0.2314 (0.7141)
AUC	126.6 (49.5, 409.2)	83.8 (17.1, 304.0)	0.0067 (0.0468)	106.9 (56.4, 304.0)	86.2 (17.1, 409.2)	0.1824 (0.7294)
IL-2 R alpha (pg/mL)						
Peak	17865.3 (4586.8, 90484.3)	10511.5 (78.0, 100000.0)	0.0064 (0.0363)	22122.3 (7878.4, 100000.0)	10994.8 (78.0, 71859.4)	0.0037 (0.0462)
AUC	232109.3 (72496.8, 1285922.7)	139029.1 (2184.0, 2069669.5)	0.0138 (0.0829)	276102.9 (129976.5, 2069669.5)	144593.7 (2184.0, 1015700.7)	0.0012 (0.0161)

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Peak is defined as the maximum postbaseline level of the cytokine.

Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28.

Original P-value is calculated by Wilcoxon rank sum test, a rank-based nonparametric test for 2 groups comparison;

Adjusted p-values are generated by a multiplicity-control procedure (Holm 's method) due to the comparisons done for each of the pre-selected cytokines in the table.

Subgroup of worst grade 2 or lower includes the subjects who did not have the event onset.

Table 11. Summary of Cytokines Peak Levels and AUC_(0-28d) in Serum with Safety Outcomes (continued)

Cytokine median(range)	Neurologic Events Subgroups			Cytokine Release Syndrome		
	With Grade 3 or higher (N = 28)	Grade 2 or lower (N = 73)	Original P-value (Adjusted p-value)	With Grade 3 or higher (N = 13)	Grade 2 or lower (N = 88)	Original P-value (Adjusted p-value)
ICAM-1 (pg/mL)						
Peak	1403139.0 (544589.3, 3625629.6)	1115066.7 (557025.0, 7495123.2)	0.1086 (0.4343)	1322829.3 (632505.6, 7495123.2)	1181890.9 (544589.3, 4588974.8)	0.1758 (0.7141)
AUC	23403848.7 (10642002.0, 64338404.7)	22629842.8 (12596507.9, 178424167.6)	0.4923 (0.9847)	27354565.3 (14464977.9, 178424167.6)	22754116.2 (10642002.0, 80536513.7)	0.0521 (0.3128)
CRP (mg/L)						
Peak	235.1 (20.6, 496.0)	198.3 (18.5, 496.0)	0.2594 (0.7782)	185.2 (20.6, 496.0)	214.9 (18.5, 496.0)	0.5458 (1.0000)
AUC	1829.7 (192.5, 7934.0)	1502.2 (150.8, 5196.9)	0.5117 (0.9847)	1753.7 (192.5, 7934.0)	1567.3 (150.8, 5196.9)	0.7037 (1.0000)
Perforin (pg/mL)						
Peak	9355.1 (2641.0, 29096.0)	11423.8 (2282.3, 47640.2)	0.2763 (0.7782)	14054.3 (4883.9, 47640.2)	10137.8 (2282.3, 32452.7)	0.1428 (0.7141)
AUC	131751.1 (42065.8, 356026.6)	196799.1 (49139.8, 1299487.2)	0.0034 (0.0337)	178593.2 (91617.5, 1299487.2)	174868.6 (42065.8, 675780.1)	0.5395 (1.0000)
IL-7 (pg/mL)						
Peak	42.2 (13.8, 153.5)	40.6 (17.7, 100.2)	0.5927 (0.7782)	40.5 (22.4, 153.5)	41.3 (13.8, 145.6)	0.9798 (1.0000)
AUC	755.9 (228.4, 3238.1)	813.3 (345.8, 1938.7)	0.2969 (0.8906)	709.8 (345.8, 2988.7)	806.4 (228.4, 3238.1)	0.5530 (1.0000)
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<p>Peak is defined as the maximum postbaseline level of the cytokine.</p> <p>Area under curve (AUC) measures the total levels of cytokine overtime, and is defined as the area under curve in a plot of levels of cytokine against scheduled visit from Baseline (ie, Day -5) to Day 28.</p> <p>Original P-value is calculated by Wilcoxon rank sum test, a rank-based nonparametric test for 2 groups comparison;</p> <p>Adjusted p-values are generated by a multiplicity-control procedure (Holm 's method) due to the comparisons done for each of the pre-selected cytokines in the table.</p> <p>Subgroup of worst grade 2 or lower includes the subjects who did not have the event onset.</p>						

6.1.2.4 Immunogenicity

The applicant reported no clinically significant effects of KTE-C19 on immune system regarding antibodies to 1) FMC63, the parent antibody from which the single chain variable region fragment (scFv) utilized in KTE-C19 is derived, and 2) (b) (4) antibodies.

Subjects with Pre-existing Antibodies to FMC63

In Study ZUMA-1, 96 of 99 evaluable subjects tested negative at baseline for antibodies against FMC63. All these 96 subjects remained negative 3 months after infusion of KTE-C19.

Three subjects tested positive at baseline for antibodies to FMC63. No differences were noted comparing these 3 subjects in KTE-C19 expansion and serum cytokine levels to the median values for the cohort. Therefore, pre-existing antibodies to FMC63 in subjects did not impact KTE-C19 pharmacokinetics and pharmacodynamics.

Anti-(b) (4) Serum (b) (4) Antibodies

The sponsor reported no evidence of immune allergic reactions in subjects with detected anti-(b) (4) antibodies.

6.1.2.5 B-cell Aplasia

Treatment of KTE-C19 may induce B-cell aplasia. The incidence of B-cell aplasia was assessed among evaluable Phase 1 and Phase 2 subjects using a qualified (b) (4) assay. As shown in Table 12, treatment of KTE-C19 induced B-cell aplasia in majority of the treated subjects.

Table 12. B-Cell Aplasia Incidence (ZUMA-1, Phase 1 and Phase 2)

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18
N	93	90	63	37	15	4	3
No B Cells	49	67	45	18	10	4	3
With B Cells	28	16	11	16	4	0	0
Undetermined*	4	3	1	0	0	0	0

*Note: Undetermined indicates that <10,000 viable leukocyte events were acquired in the (b) (4) assay.

6.1.2.6 Replication-competent Retrovirus (RCR)

KTE-C19 comprises retroviral vector transduced T cells, the presence of replication-competent retrovirus (RCR) in the blood of treated subjects were monitored. No subjects were found to be RCR positive.

6.1.3 Conclusions

- Following infusion of KTE-C19 in patients with relapsed or refractory large B-cell lymphoma, KTE-C19 exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of KTE-C19 occurred within the first 7-14 days after KTE-C19 infusion.
- After infusion, the median values of C_{max} and AUC_(0-28d) of KTE-C19 in responders [complete response (CR) and partial response (PR)] were about 2-fold of C_{max} and AUC_(0-28d) in non-responders.
- Subjects with Grade 3 or higher neurologic events had significantly higher KTE-C19 expansion (C_{max} and AUC_(0-28d)) compared to subjects with Grade 2 or lower neurologic events.
- Compared to subjects with Grade 2 or lower neurologic events, subjects with Grade 3 or higher cytokine release syndrome (CRS) had higher KTE-C19 AUC_(0-28d), but not for peak levels of KTE-C19. The difference in AUC_(0-28d) was not statistically significant.
- Age (range: 23 – 76 years old) and gender had no significant impact on AUC_(0-28d) and C_{max} of KTE-C19.
- Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with KTE-C19. KTE-C19 continued expansion in subjects who received tocilizumab and corticosteroids after infusion of KTE-C19.
- After KTE-C19 infusion, peak levels and AUC_(0-28d) of a number of biomarkers were significantly higher in subjects with Grade 3 or higher neurologic events than subjects with Grade 2 or lower neurologic events. These biomarkers include IL-15, IL-6, IL-2R α , IL-8, IL-10, IFN- γ , TNF- α , IP-10, IL-2, ferritin, and IL-1RA.

- Significantly elevated peak levels and $AUC_{(0-28d)}$ were reported in subjects developed Grade 3 or higher CRS compared to subjects with Grade 2 or lower CRS for following biomarkers: IL-15, IL-6, IL-2R α , IL-10, IFN- γ , TNF- α , Granzyme B, IP-10, and IL-1RA.
- KTE-C19 induced B-cell aplasia in majority of the treated subjects. And KTE-C19 induced B-cell aplasia lasted for a period of time.
- There was no reported presence of replication-competent retrovirus (RCR) in the blood of treated subjects.