Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Clinical Pharmacology BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology

Office of Tissues and Advanced Therapy

BLA	125643/394
Product	YESCARTA (axicabtagene ciloleucel, Axicel, KTE-C19), Cell suspension
Sponsor	Kite Pharma, Inc.
Indication	Treatment of adult patients with relapsed or refractory large B-cell lymphoma (r/r LBCL) within 12 months of first line chemoimmunotherapy
Date Received	09/30/2021
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

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

On September 30, 2021, Kite Pharma Inc. submitted a Prior Approval Supplement (PAS) seeking an additional indication for YESCARTA® (axicabtagene ciloleucel, axicel, KTE-C19) for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma (LBCL) within 12 months of first line chemoimmunotherapy. The proposed dosing regimen is 2.0×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2.0×10^8 CAR-positive viable T cells in approximately 68 mL to be infused intravenously in adult patients.

YESCARTA® was approved for 1) the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy on October 18, 2017; and 2) the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy on April 02, 2021.

The clinical pharmacology section of this PAS is supported by one Phase 3, randomized, open-label, multicenter study to determine the efficacy, safety, pharmacokinetics and pharmacodynamics of YESCARTA® in adult patients with relapsed/refractory diffuse large B-cell lymphoma (LBCL) after first line chemoimmunotherapy (Study # KTE-C19-107, ZUMA-7).

The proposed dosing regimen for YESCARTA® administered by intravenous (IV) infusion has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable in adult subjects with relapsed/refractory large B-cell lymphoma within 12 months of first line chemoimmunotherapy. From a clinical pharmacology standpoint, the PAS is acceptable to support approval.

2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Following are key clinical pharmacology findings of YESCARTA (axicabtagene ciloleucel, axicel, KTE-C19)[1] in adult subjects with relapsed or refractory (r/r) large B-cell lymphoma (LBCL) after first line chemoimmunotherapy:

- After the initial single dose infusion, axicel exhibited an initial rapid expansion phase followed by bi-phasic decline. After infusion on Day 0, axicel achieved peak levels in peripheral blood around Day 7 (range 2 to 233 days).

- As of data cutoff date, axicel was detected in peripheral blood in some subjects up to 24 months post-infusion, demonstrating long term persistence.

[1] In this review, YESCARTA is also referred to as axicel.

- Higher percentages of viable CAR T-cells in the final product were potentially associated with increased expansion of axicel in adult subjects with r/r LBCL.

- Higher exposure of axicel was observed in responding [complete response (CR) + partial response (PR)] subjects, compared to non-responding subjects [stable disease (SD) + progressive disease (PD)]. The median $AUC_{0\text{-}28d}$ and Cmax in responding subjects were 418% and 277% of those in nonresponding subjects, respectively.

- Higher axicel exposure were observed in subjects with Grade 2 or higher cytokine release syndrome (CRS). The median $AUC_{0\text{-}28d}$ and Cmax in subjects with Grade 2 or higher CRS were 216% and 156% of those in subjects with Grade 1 or no CRS.

- Higher axicel exposure were associated with severe neurologic events (sNE) (≥ Grade 3). The median $AUC_{0\text{-}28d}$ and Cmax in subjects with Grade 3 or higher neurologic events were 216% and 146% of those in subjects with Grade 2, Grade 1 or no neurologic events.

- Higher axicel exposure (Cmax and $AUC_{0\text{-}28d}$) was observed in subjects administered tocilizumab and/or corticosteroids for management of CRS and/or neurologic events (NE) than in subjects who did not take tocilizumab or corticosteroids for management of CRS and/or NE. The observations correspond to the observation that higher axicel expansion levels are associated to more severe adverse events that require management with medications. Axicel continued to expand in subjects who received tocilizumab and corticosteroids.

- Compared to subjects with Grade 2, Grade 1 or no CRS, substantially higher peak serum levels were observed in subjects who developed Grade 3 or higher CRS for the following biomarkers: CXCL10, ferritin, granzyme B, ICAM-1, IL-2Rα, IL-6, IL-10, IL-15, VCAM-1, GM-CSF, IL-17, and MCP-1. Higher median AUC values were observed in subjects who developed Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following biomarkers: ferritin, granzyme B, IL-2Rα, IL-6, IL-15, VCAM-1, GM-CSF, IL-17, and VEGF.

- Compared to subjects with Grade 2, Grade 1 or no neurologic events, substantially higher peak serum levels and AUC values were reported in subjects who developed Grade 3 or higher neurologic events for the following biomarkers: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IFN-γ, IL-2Rα, IL-6, IL-10, IL-15, and VCAM-1. For IL-2, and IL-5, higher peak serum levels, but not AUC values were observed in subjects with Grade 3 or higher NE compared to subjects with Grade 2, Grade 1 or no neurologic events.

- Compared to subjects who experienced Grade 2, Grade 1, or no neurologic events after infusion of axicel, subjects with Grade 3 or higher neurologic events had ≥ 2-fold higher cerebrospinal fluid (CSF) levels of CRP, ferritin, granzyme B, IFN-γ, IL-2Rα, MCP-1, and SAA.

- At Month 3 post-infusion, the percentage of subjects with B-cell aplasia increased from 42.5% (baseline) to 62.3% in the evaluable subjects. B-cell recovery was observed at Month 9 post-infusion, and continued through Month 24.

- Responding subjects with undetectable B-cell levels had higher median CAR T-cell levels than non-responding subjects with detectable B-cell levels from Month 3 to Month 24.

- Immunogenicity was assessed 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 axicel was developed. There were no positive results based on the confirmatory cell-based assay.

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

3 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125643/394 and finds it acceptable pending the following revisions shown below.

Reviewer's Comments to the Applicant:

Please move the ZUMA-1 section ahead of ZUMA-7 section to maintain consistency with the indication statements.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

YESCARTA, 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 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 sIL2Rα 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.
LBCL

Among patients with LBCL with an ongoing response at 24 months in the ZUMA-7 study, 21 of 61 evaluable patients (34%) had no detectable B cells at baseline, and the majority of patients at Month 3 (43 of 69 evaluable patients [62%]) and Month 6 (8 of 13 evaluable patients [62%]) had no detectable B cells. At Month 24, 20 of 24 evaluable patients (83%) had detectable B cells.

Among evaluable LBCL patients with an ongoing response at 24 months in the ZUMA-1 study, 45% had no detectable B cells at baseline, and a majority of subjects at Month 3 (80%) and Month 6 (78%) had no detectable B cells. At Month 24, 75% of subjects had detectable B cells.

12.3. Pharmacokinetics

Following infusion of YESCARTA, 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: 21 – 80 years) and gender had no significant impact on AUC Day 0 - 28 and C_{max} of YESCARTA.

LBCL
Among patients with LBCL in the ZUMA-7 study (n=162 evaluable), the number of anti-CD19 CAR T cells in blood was positively associated with objective response [complete remission (CR) or partial remission (PR)]. The median anti-CD19 CAR T cell C_{max} levels in responders (n=142) were 275% higher compared to the corresponding level in nonresponders (n=20) (28.9 cells/µL vs 10.5 cells/µL). Median AUC Day 0 - 28 in responding patients (n=142) was 418% of the corresponding level in nonresponders (n=20) (292.9 days × cells/µL vs. 70.1 days × cells/µL).

Among patients with LBCL in the ZUMA-1 study (n=96 evaluable), 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/µL vs 21.2 cells/µL). Median AUC Day 0 - 28 in responding patients (n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days × cells/µL vs. 222.0 days × cells/µL).

FL

Among patients with FL in the ZUMA-5 study (n=81 evaluable), the median anti-CD19 CAR T-cell C_{max} levels in responders (n=74) were 40.1 cells/µL and 46.0 cells/µL in nonresponders (n=7). The median AUC Day 0 - 28 in responding FL patients (n=74) were 465.8 days × cells/µL and 404.5 days × cells/µL in nonresponders (n=7).

Some patients required tocilizumab and corticosteroids for management of CRS and neurologic toxicities. Patients treated with tocilizumab (n=44) had 262% and 232% higher anti-CD19 CAR T cells as measured by AUC Day 0 - 28 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 Day 0 - 28 and C_{max} compared to patients who did not receive corticosteroids (n=75).

Hepatic and renal impairment studies of YESCARTA 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 3, randomized, open-label study evaluating the efficacy of axicabtagene ciloleucel (axicel, KTE-C19) versus standard of care therapy in subjects with relapsed/refractory (r/r) diffuse large B-cell lymphoma (LBCL) (Study No. KTE-C19-107, ZUMA-7)

Clinical Pharmacology-Related Objectives

	Pharmacokinetics	Pharmacodynamics	Other
Objectives	• Characterize the presence, expansion, and persistence of anti-CD19 CAR T cells in blood • Explore associations between pharmacokinetic profile versus clinical efficacy and safety outcomes • Describe pharmacokinetic profile by cell of origin, disease diagnosis subtype and prognostic subgroups	• Characterize levels of serum and CSF analytes at baseline, after lymphodepleting chemotherapy, prior to and after infusion of axicabtagene ciloleucel • Explore associations between serum analyte profiles versus safety outcomes • Summarize B-cell aplasia and recovery, and their association with pharmacokinetic and clinical response endpoints	• Describe key product attributes and explore their association with pharmacokinetics, clinical efficacy, and safety outcomes • Describe product attributes based on exhausted T-cell markers • Explore characteristics of the tumor and product to elucidate mechanisms of resistance and relapse to axicabtagene ciloleucel
Endpoints	• Levels of anti-CD19 CAR T cells in blood samples measured as anti-CD19 CAR^+ cells/µL by visit, peak, $AUC_{0\text{-}28}$ (from infusion to Week 4 post-treatment after infusion), and time-to-peak	• Levels of cytokines in serum by visit, AUC, and time-to-peak • B cell as percent of viable leukocyte tested over time • Levels of CSF analytes after infusion[a]	• Product attributes measurements after product manufacturing and prior to dosing • Cell of origin classification at screening • Product attributes measurements based on T cell exhaustion flow cytometry panel

Source: Applicant. Clinical study report KTE-C19-107 (ZUMA-7).

Study Design

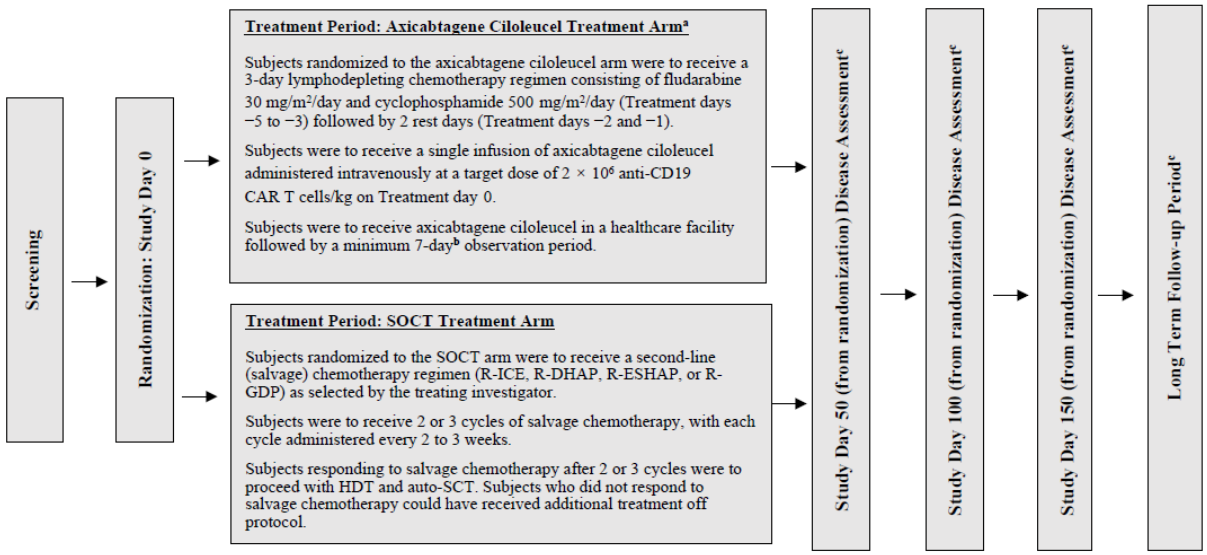
ZUMA-7 is a Phase 3, multicenter, open-label study evaluating the efficacy of axicel versus standard of care therapy (SOCT) in subjects with r/r LBCL after first line chemoimmunotherapy.

As shown in Figure 1, ZUMA-7 is a randomized study comparing axicel with SOCT (ie, salvage chemotherapy followed by high-dose therapy-auto-stem cell transplant). Adult subjects with r/r LBCL after first-line rituximab and anthracycline-based chemotherapy were randomized in a 1:1 ratio to receive axicel or SOCT.

For subjects in the axicel arm, treatment consisted of leukapheresis, lymphodepleting chemotherapy followed by a single intravenous infusion of axicel. The lymphodepleting

regimen consisted of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the fifth, fourth, and third day before infusion of axicel.

Figure 1. Study Schema



Abbreviations: auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; HDT, high-dose therapy; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOCT, standard of care therapy; Study Day, number of days from the day of randomization; Treatment day, number of days from the day of axicabtagene ciloleucel treatment.

a At the discretion of the investigator, corticosteroid bridging therapy could have been considered for subjects with high disease burden at screening.

b Minimum observation period: 7 days unless otherwise required by country regulatory agencies (eg, 10 days for subjects treated in Germany, Switzerland, and France).

c Disease assessments were to be calculated from the date of randomization and not the date of dosing with axicabtagene ciloleucel or SOCT. Independent of the treatment arm, study procedures and disease assessments were to occur at the same protocol-defined timepoints.

Source: Applicant. Clinical study report KTE-C19-107 (ZUMA-7).

The dose selection of axicel for this study was based on the overall favorable analysis of the benefit-risk in Study KTE-C19-101 (ZUMA-1): a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, and a maximum flat dose of axicel 2 x 10^8 anti-CD19 CAR T cells was used in this study.

For pharmacokinetic analyses, blood samples were collected prior to initiation of lymphodepleting chemotherapy or pre-infusion (baseline), and at 1, 3, 7, 14, 28 days, and 3, 6, 9, 12, 18, and 24 months post-infusion. Blood levels of axicel were monitored by a validated quantitative polymerase chain reaction (qPCR) assay, which is specifically designed for measuring cells with a stable integrated anti-CD19 CAR transgene.

Blood samples were also obtained for pharmacodynamics biomarker analysis at the following time points: prior to initiation of lymphodepleting chemotherapy (baseline), pre-infusion on infusion day (pre-dose), and at 1, 3, 5, 7, 14, and 28 days, and 3 and 6 months post-infusion.

5.1.2 Results

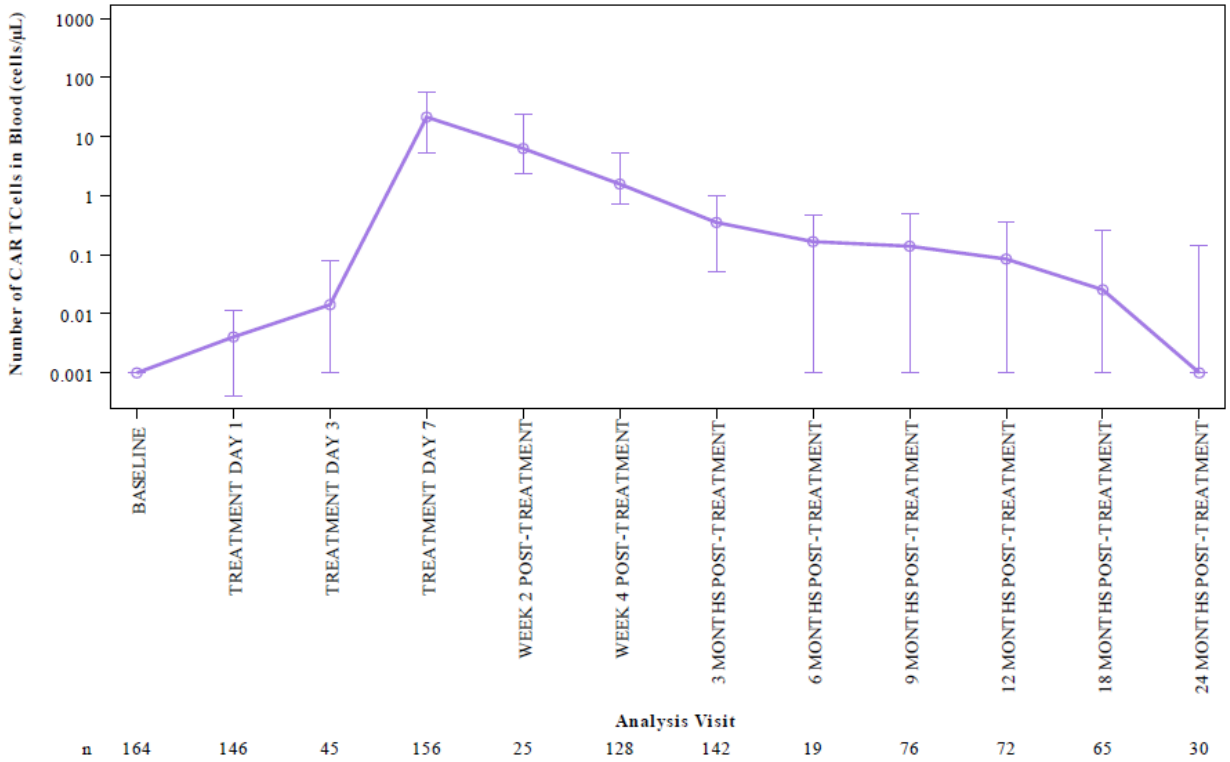
5.1.2.1 Pharmacokinetics

General Pharmacokinetic Characteristics for All Treated Subjects

With the data cut-off date of March 18, 2021, a total of 170 subjects with r/r LBCL were treated with axicel in Study ZUMA-7. A total of 162 subjects had measurable anti-CD19 CAR T cells in the peripheral blood within the first 28 days after administration.

After the initial single dose infusion of axicel (Day 0), axicel exhibited an initial rapid expansion phase followed by bi-phasic decline. After infusion, axicel achieved peak levels in peripheral blood around Day 7 (range: 2 to 233 days). The median peak level of axicel CAR T cells was 25.84 cells/µL (range: 0.04 to 1173.25 cells/µL) and median $AUC_{0\text{-}28d}$ was 236.23 days*cells/µL (range: 0.0 to 1.65 x 10^4 days*cells/µL). By Month 3, median levels of axicel in blood decreased towards baseline in evaluable subjects (median: 0.35 cells/µL; range: 0.00 to 28.44 cells/µL). By 24 months post-infusion, axicel was detected in peripheral blood in 12 out of 30 evaluable subjects (Table 1, Figure 2).

Figure 2. Pharmacokinetic Profile of Axicel in Peripheral Blood (Median, (Q1, Q3))



Source: Applicant. Pharmacokinetic and Pharmacodynamic Report for ZUMA-7.

Table 1. Summary of Axicel Pharmacokinetic Parameters

	Axicabtagene Ciloleucel (N = 170)
Peak (cells/μL)	
n	162
Mean (STDEV)	58.19 (118.50)
Median (Q1, Q3)	25.84 (8.15, 57.93)
Min, Max	0.04, 1173.25
AUC_{0-28} (cells/μL*days)	
n	162
Mean (STDEV)	730.51 (1650.99)
Median (Q1, Q3)	236.23 (76.36, 757.96)
Min, Max	0.00, 1.65E+04
Time to peak (days)	
n	162
Mean (STDEV)	15.79 (24.94)
Median (Q1, Q3)	8 (8, 9)
Min, Max	2, 233

Source: Applicant. Pharmacokinetic and Pharmacodynamic Report for ZUMA-7.

Factors Impacting Axicel Pharmacokinetics

The following factors were evaluated for potential impact on axicel pharmacokinetics: age, sex, race, ethnicity, baseline tumor burden, disease type, molecular subgroup, geographic region, ECOG performance status, response to first-line therapy, second-line age-adjusted IPI, double-hit/triple-hit/double expressor status, baseline CD19 H-score and CD19 positive status. None of above factors had statistically significant impact on the pharmacokinetic profile of axicel.

Product Characteristics and Axicel Pharmacokinetic Profiles

The association between axicel product characteristics and pharmacokinetics was evaluated. Analysis suggested potential association between (b) (4) and post-infusion peak levels of axicel (Table 2).

Table 2. Axicel Product Characteristics and Post-infusion Peak Levels

Product Characteristic	Axicabtagene Ciloleucel (N = 170)		
	Number of Evaluable Subjects	Regression Coefficient (95% CI)	P-value
(b) (4)			

Source: Applicant. Pharmacokinetic and Pharmacodynamic Report for ZUMA-7.

Pharmacokinetics in Retreatment Subjects

Nine subjects received a second dose of axicel and 8 subjects had evaluable PK profiles. Compared to the first dose of axicel, the exposures of axicel after the second dose were substantially lower (Table 3). After retreatment, 5 subjects had a response (CR).

Table 3. Pharmacokinetics of Axicel in Subjects with Retreatment of Axicel (N=8)

Parameters Median (Q1, Q3) (range)	First Treatment	Second Treatment
$AUC_{0\text{-}28d}$ (days*cells/μL)	393.74 (202.54, 918.05) (136.14, 16,484.28)	72.48 (36.33, 93.24) (0.01, 126.86)
Cmax (cells/μL)	26.82 (13.63, 66.36) (9.35, 1,173.25)	4.79 (3.05, 10.47) (0.03, 52.11)
Tmax (days)*	8.00 (8.00, 8.00)	8.00 (2.00, 30.00)

*Median (range)

5.1.2.2 Pharmacodynamics

Serum Pharmacodynamic Biomarkers

A panel of 29 serum biomarkers, including cytokines, chemokines and immune effector-related biomarkers were monitored longitudinally till 4 weeks post-infusion of axicel: CRP, CXCL10, ferritin, granzyme B, ICAM-1, IFN-γ, IL-1RA, IL-2, IL-2Rα, IL-6, IL-7, IL-8, IL-10, IL-15, TNF-α, VCAM-1, GM-CSF, IL-12 P40, IL-17, IL-4, IL-5, MCP-1, MCP-4, MDC, MIP-1α, MIP-1β, SAA, TARC, and VEGF.

After lymphodepleting chemotherapy and prior to infusion of axicel, median serum levels of IL-15 and MCP-1 increased by ≥ 2-fold, and median serum levels of granzyme B, IL-12 P40, IL-17, and MDC decreased by ≤ 2-fold relative to baseline levels.

After axicel infusion, peak levels of majority key analytes were achieved within 7 days after axicel infusion. Levels of the majority of serum analytes returned to baseline levels by 4-weeks post-infusion.

The applicant conducted correlative analysis to explore potential associations between serum biomarkers and adverse events such as CRS and neurologic events. The following potential associations were observed based on Wilcoxon rank sum test ($p \leq 0.05$):

- compared to subjects with Grade 2, Grade 1 or no CRS, substantially higher peak serum levels were observed in subjects who developed Grade 3 or higher CRS for the following biomarkers: CXCL10, ferritin, granzyme B, ICAM-1, IL-2Rα, IL-6, IL-10, IL-15, VCAM-1, GM-CSF, IL-17, and MCP-1. Higher median AUC values were observed in subjects who developed Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following biomarkers: ferritin, granzyme B, IL-2Rα, IL-6, IL-15, VCAM-1, GM-CSF, IL-17, and VEGF.

- Compared to subjects with Grade 2, Grade 1 or no neurologic events, substantially higher peak serum levels and AUC values were reported in subjects who developed Grade 3 or higher neurologic events for the following biomarkers: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IFN-γ, IL-2Rα, IL-6, IL-10, IL-15, and VCAM-1. For IL-2, and IL-5, higher peak serum levels, but not AUC values were observed in subjects with Grade 3 or higher NE compared to subjects with Grade 2, Grade 1 or no neurologic events.

Cerebrospinal Fluid Pharmacodynamic Biomarkers

A panel of 40 biomarkers were analyzed in available cerebrospinal fluid (CSF) samples. Compared to subjects who experienced Grade 2, Grade 1, or no neurologic events after infusion of axicel, subjects with Grade 3 or higher neurologic events had ≥ 2-fold higher CSF levels of CRP, ferritin, granzyme B, IFN-γ, IL-2Rα, MCP-1, and SAA.

B-Cell Aplasia

Treatment of axicel may result in B-cell aplasia. The incidence of B-cell aplasia was assessed in Study ZUMA-7 using a flow cytometry assay. As shown in Table 4, B-cell aplasia was observed in 42.5% of the evaluable subjects at baseline. At Month 3 post-infusion, the percentage of subjects with B-cell aplasia increased to 62.3% in the evaluable subjects. The median B-cell levels at Month 3 was similar to baseline. B-cell recovery was observed at Month 9 post-infusion, detectable B-cell levels were observed in 58.4% of evaluable subjects and the median B-cell level increased to 9.79% (range: 0.04% to 52.88%). B-cell recovery continued through Month 24.

Table 4. B-cell Recovery Following Axicel Infusion

B-cell Levels (%)[a]	Axicabtagene Ciloleucel (N = 170)
Baseline	
n	141
n (B cells below LLOQ)	60
n (B cells detectable)	81
Mean (STDEV)	2.43 (5.09)
Median (Q1, Q3)	0.27 (0.05, 2.00)
Min, Max	0.02, 32.18
3 Months Post-treatment	
n	138
n (B cells below LLOQ)	86
n (B cells detectable)	52
Mean (STDEV)	3.62 (6.67)
Median (Q1, Q3)	0.37 (0.06, 3.22)
Min, Max	0.02, 24.51
6 Months Post-treatment	
n	17
n (B cells below LLOQ)	10
n (B cells detectable)	7
Mean (STDEV)	8.26 (8.98)
Median (Q1, Q3)	4.02 (0.13, 17.65)
Min, Max	0.04, 23.00
9 Months Post-treatment	
n	77
n (B cells below LLOQ)	32
n (B cells detectable)	45
Mean (STDEV)	12.37 (12.47)
Median (Q1, Q3)	9.79 (0.17, 22.75)
Min, Max	0.02, 49.60
12 Months Post-treatment	
n	73
n (B cells below LLOQ)	34
n (B cells detectable)	39
Mean (STDEV)	15.95 (13.44)
Median (Q1, Q3)	14.56 (1.35, 23.76)
Min, Max	0.04, 52.88
18 Months Post-treatment	
n	61
n (B cells below LLOQ)	22
n (B cells detectable)	39
Mean (STDEV)	17.75 (13.06)
Median (Q1, Q3)	16.03 (7.90, 27.17)
Min, Max	0.03, 54.77
24 Months Post-treatment	
n	26
n (B cells below LLOQ)	4
n (B cells detectable)	22
Mean (STDEV)	19.99 (14.86)
Median (Q1, Q3)	18.55 (12.49, 28.96)
Min, Max	0.02, 48.99

Source: Applicant. Pharmacokinetic and Pharmacodynamic Report for ZUMA-7.

Analysis was conducted to explore the potential relationship between B-cell aplasia and CAR T-cell levels by subjects' ongoing response (Table 5). Responding subjects with undetectable B-cell levels had higher median CAR T-cell levels than non-responding subjects with detectable B-cell levels from Month 3 to Month 24.

Table 5. Summary of B-cell Aplasia and Axicel Persistence Over Time by Ongoing Response

	Axicabtagene Ciloleucel (N = 170)								
	Ongoing Response (N = 75)			Relapsed (N = 66)			Nonresponders (N = 21)		
	n (%)	B Cells (%)[a] Median (Min, Max)	CAR T Cells (cells/µL) Median (Min, Max)	n (%)	B Cells (%)[a] Median (Min, Max)	CAR T Cells (cells/µL) Median (Min, Max)	n (%)	B Cells (%)[a] Median (Min, Max)	CAR T cells (cells/µL) Median (Min, Max)
Baseline									
All subjects	61 (81.33)	0.24 (0.02, 18.94)	0.00 (0.00, 0.00)	59 (89.39)	0.28 (0.02, 32.18)	0.00 (0.00, 0.00)	16 (76.19)	0.60 (0.04, 1.82)	0.00 (0.00, 0.00)
B cells ≤ LLOQ	21 (34.43)		0.00 (0.00, 0.00)	27 (45.76)		0.00 (0.00, 0.00)	9 (56.25)		0.00 (0.00, 0.00)
B cells detectable	40 (65.57)	0.24 (0.02, 18.94)	0.00 (0.00, 0.00)	32 (54.24)	0.28 (0.02, 32.18)	0.00 (0.00, 0.00)	7 (43.75)	0.60 (0.04, 1.82)	0.00 (0.00, 0.00)
3 Months Post-treatment									
All subjects	69 (92.00)	0.57 (0.02, 24.51)	0.35 (0.00, 28.44)	57 (86.36)	0.16 (0.02, 23.21)	0.39 (0.00, 16.56)	7 (33.33)	0.17 (0.17, 0.17)	0.17 (0.00, 0.59)
B cells ≤ LLOQ	43 (62.32)		0.45 (0.00, 28.44)	35 (61.40)		0.61 (0.00, 13.62)	6 (85.71)		0.19 (0.00, 0.59)
B cells detectable	26 (37.68)	0.57 (0.02, 24.51)	0.13 (0.00, 3.66)	22 (38.60)	0.16 (0.02, 23.21)	0.04 (0.00, 16.56)	1 (14.29)	0.17 (0.17, 0.17)	0.17 (0.17, 0.17)
6 Months Post-treatment									
All subjects	13 (17.33)	9.71 (0.13, 23.00)	0.17 (0.00, 14.91)	4 (6.06)	1.67 (0.04, 3.31)	0.19 (0.00, 1.08)	0		
B cells ≤ LLOQ	8 (61.54)		0.37 (0.00, 14.91)	2 (50.00)		0.63 (0.19, 1.08)	0		
B cells detectable	5 (38.46)	9.71 (0.13, 23.00)	0.00 (0.00, 0.01)	2 (50.00)	1.67 (0.04, 3.31)	0.00 (0.00, 0.00)	0		
9 Months Post-treatment									
All subjects	57 (76.00)	9.15 (0.02, 49.60)	0.13 (0.00, 2.95)	19 (28.79)	13.58 (0.08, 30.49)	0.30 (0.00, 1.98)	1 (4.76)		0.36 (0.36, 0.36)
B cells ≤ LLOQ	20 (35.09)		0.51 (0.08, 2.95)	11 (57.89)		0.62 (0.10, 1.98)	1 (100.00)		0.36 (0.36, 0.36)
B cells detectable	37 (64.91)	9.15 (0.02, 49.60)	1.32E-03 (0.00, 0.88)	8 (42.11)	13.58 (0.08, 30.49)	0.00 (0.00, 0.42)	0		
12 Months Post-treatment									
All subjects	55 (73.33)	14.56 (0.06, 52.88)	0.05 (0.00, 2.36)	18 (27.27)	14.30 (0.04, 27.96)	0.37 (0.00, 1.16)	0		
B cells ≤ LLOQ	22 (40.00)		0.24 (0.05, 2.36)	12 (66.67)		0.67 (0.11, 1.16)	0		
B cells detectable	33 (60.00)	14.56 (0.06, 52.88)	0.00 (0.00, 1.40)	6 (33.33)	14.30 (0.04, 27.96)	0.00 (0.00, 0.35)	0		
18 Months Post-treatment									
All subjects	55 (73.33)	16.03 (0.03, 54.77)	5.15E-03 (0.00, 2.57)	6 (9.09)	10.61 (0.14, 21.08)	0.56 (0.00, 2.38)	0		

	Axicabtagene Ciloleucel (N = 170)								
	Ongoing Response (N = 75)			Relapsed (N = 66)			Nonresponders (N = 21)		
	n (%)	B Cells (%)[a] Median (Min, Max)	CAR T Cells (cells/µL) Median (Min, Max)	n (%)	B Cells (%)[a] Median (Min, Max)	CAR T Cells (cells/µL) Median (Min, Max)	n (%)	B Cells (%)[a] Median (Min, Max)	CAR T cells (cells/µL) Median (Min, Max)
B cells ≤ LLOQ	18 (32.73)		0.33 (0.03, 2.57)	4 (66.67)		0.56 (0.15, 2.38)	0		
B cells detectable	37 (67.27)	16.03 (0.03, 54.77)	0.00 (0.00, 0.64)	2 (33.33)	10.61 (0.14, 21.08)	0.99 (0.00, 1.98)	0		
24 Months Post-treatment									
All subjects	24 (32.00)	19.69 (0.02, 48.99)	0.00 (0.00, 1.29)	2 (3.03)	9.89 (0.03, 19.75)	0.07 (8.35E-03, 0.14)	0		
B cells ≤ LLOQ	4 (16.67)		0.43 (0.14, 1.29)	0			0		
B cells detectable	20 (83.33)	19.69 (0.02, 48.99)	0.00 (0.00, 1.04)	2 (100.00)	9.89 (0.03, 19.75)	0.07 (8.35E-03, 0.14)	0		

Source: Applicant. Pharmacokinetic and Pharmacodynamic Report for ZUMA-7.

5.1.2.3 Exposure-Response Relationship

Exposure-Response for Efficacy

The relationship between axicel exposure and efficacy was evaluated. As shown in Table 6, higher exposure of axicel was observed in responding [complete response (CR) + partial response (PR)] subjects, compared to non-responding subjects [stable disease (SD) + progressive disease (PD)]. The median $AUC_{0\text{-}28d}$ and Cmax in responding subjects were 418% and 277% of those in nonresponding subjects, respectively (Wilcoxon rank sum test p= 0.0054 and p=0.0224 for $AUC_{0\text{-}28d}$ and Cmax, respectively).

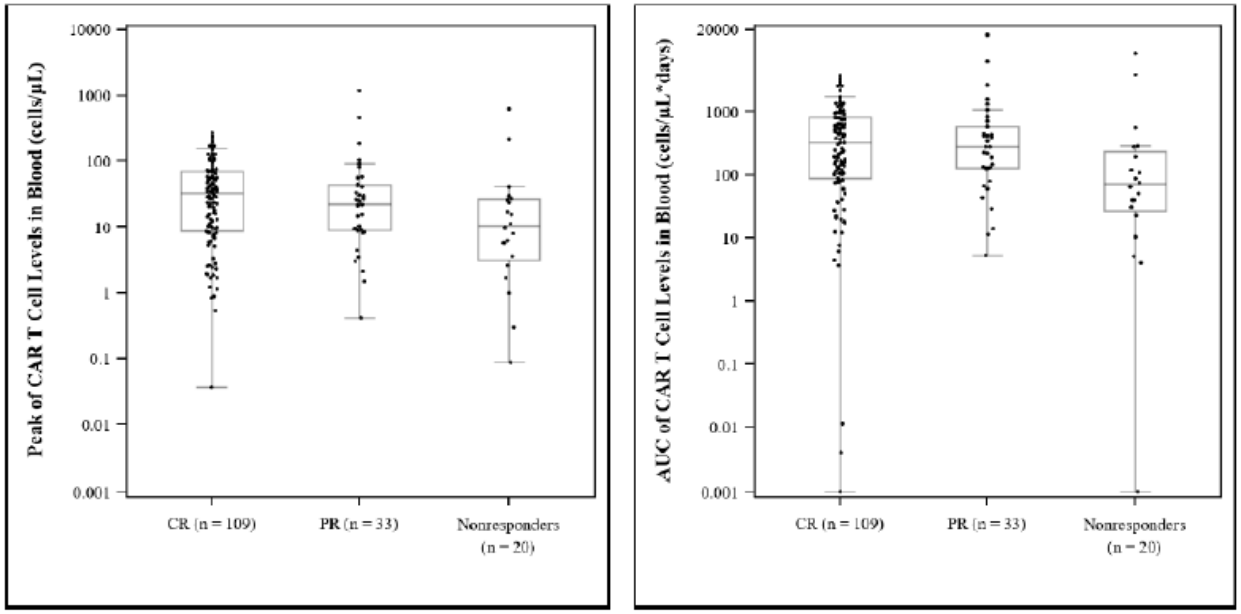
Table 6. Comparison of Axicel Expansion Between Responding and Non-responding Subjects

	Axicabtagene Ciloleucel (N = 170)	
	Responders (CR + PR) (N = 149)	Nonresponders (SD+PD) (N = 21)
Peak (cells/µL)		
n	142	20
Mean (STDEV)	58.87 (115.40)	53.40 (141.90)
Median (Q1, Q3)	28.94 (8.64, 65.33)	10.45 (3.11, 26.18)
Min, Max	0.04, 1173.25	0.09, 622.50
AUC_{0-28} (cells/µL*days)		
n	142	20
Mean (STDEV)	732.21 (1599.65)	718.44 (2026.71)
Median (Q1, Q3)	292.86 (88.86, 810.28)	70.14 (26.91, 234.20)
Min, Max	0.00, 1.65E+04	0.00, 8541.63
Time to Peak (Days)		
n	142	20
Mean (STDEV)	15.52 (25.16)	17.70 (23.87)
Median (Q1, Q3)	8 (8, 8)	8 (8, 15)
Min, Max	2, 233	8, 106

Source: Applicant. Pharmacokinetic and Pharmacodynamic Report for ZUMA-7.

Comparison among subjects' best overall response indicated that axicel exposures were similar between subjects with complete response (CR) and subjects with partial response (PR). However, the axicel exposure in subjects with CR was significantly higher than that in non-responding subjects (Wilcoxon rank sum test p= 0.0201 and p=0.0501 for AUC_{0-28d} and Cmax, respectively) (Figure 3)

Figure 3. Axicel Exposure and Best Overall Responses

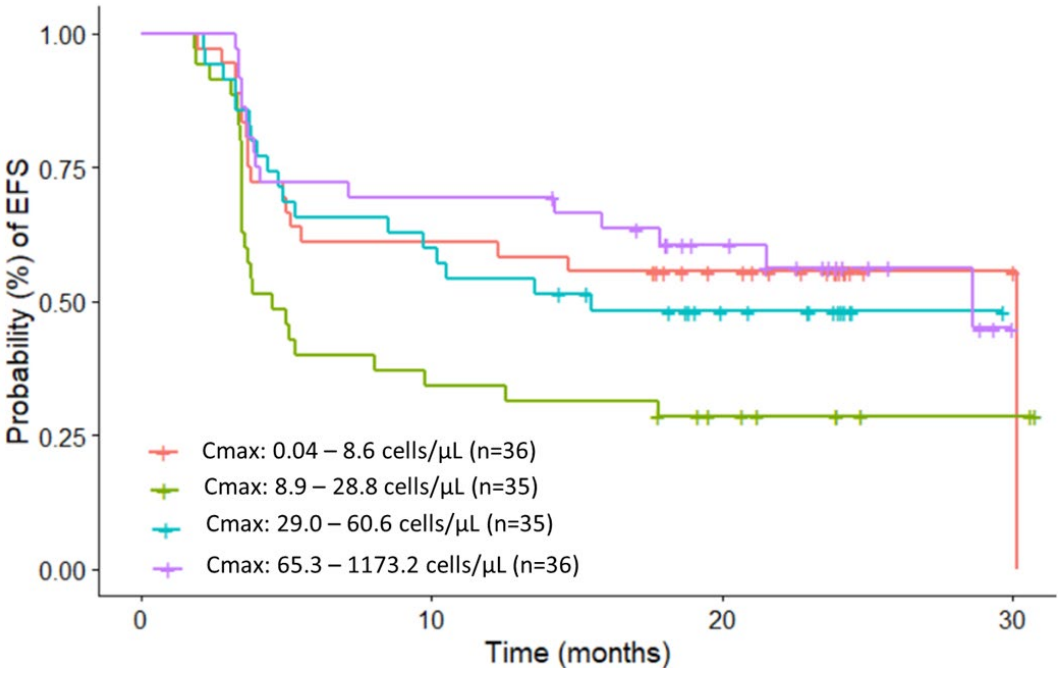


Source: Applicant. Pharmacokinetic and Pharmacodynamic Report for ZUMA-7.

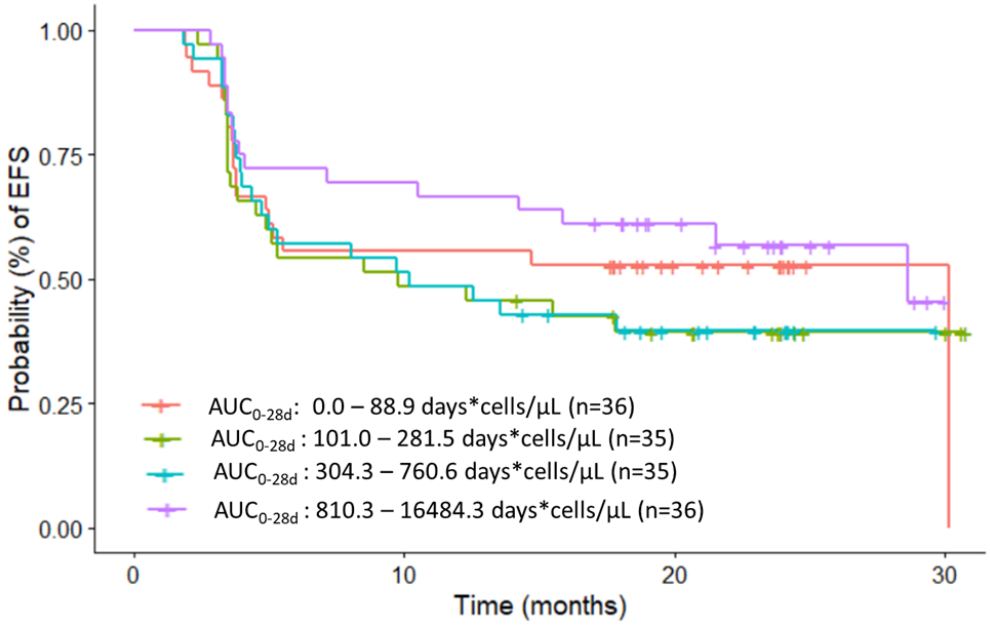
Figure 4 shows Kaplan-Meier curves of event-free survival (EFS) by quantile analysis of axicel exposure ($AUC_{0\text{-}28d}$ and Cmax). It is observed that the highest quantile of axicel exposure may be associated with longer EFS. However, cox proportional-Hazard analysis did not show significant correlation between axicel exposure and EFS.

Figure 4. Kaplan-Meier Curve of Event-free Survival (EFS) by Axicel Exposure Quantile Groups

a. Cmax



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



Exposure-Response for Safety

Exposure and Cytokine Release Syndrome (CRS)

The potential relationship between axicel exposure on cytokine release syndrome (CRS) was evaluated. Due to the small sample size of subjects with severe CRS (≥ Grade 3), comparison was performed between subjects with Grade 2 or higher CRS and subjects with Grade 1 or no CRS. As shown in Table 7, subjects with Grade 2 or higher CRS tended to have higher axicel exposure, compared to subjects with Grade 1 or no CRS.

Table 7. Summary of Axicel Exposure and Cytokine Release Syndrome

Parameters Median (Q1, Q3) (range)	**Grade ≥ 2 (N=84)**	**Grade ≤ 1 (N=78)**	p-value*
$AUC_{0\text{-}28d}$ (days*cells/µL)	357.91 (102.15, 975.08) (0.00, 16,484.28)	165.40 (45.22, 580.44) (0.00, 6,223.76)	0.0466*
Cmax (cells/µL)	29.21 (9.18, 77.22) (0.04, 1,173.25)	18.67 (5.81, 54.87) (0.30, 459.76)	0.1074
Tmax (days)	8.00 (2.00, 106.00)	8.00 (4.00, 233.00)	--

*Wilcoxon rank sum test

Exposure and Neurologic events

Potential association between axicel exposure and risks of severe neurologic events (NE) (≥ Grade 3) was evaluated. Subjects with Grade 3 or higher neurologic events had substantially higher axicel exposure than subjects with Grade 2, Grade 1 or no neurologic events (Table 8).

Table 8. Summary of Axicel Exposure and Neurologic events

Parameters Median (Q1, Q3) (range)	**Grade ≥3 (N=40)**	**Grade ≤2 (N=122)**	**p-value#**
$AUC_{0\text{-}28d}$ (days*cells/μL)	438.59 (122.98, 970.73) (28.78, 16,484.28)	203.32 (53.07, 633.32) (0.00, 8,541.63)	0.0251*
Cmax (cells/μL)	34.20 (11.97, 80.53) (3.05, 1,173.25)	23.49 (6.98, 55.19) (0.04, 622.50)	0.0703
Tmax (days)	8.00 (2.00, 35.00)	8.00 (4.00, 233.00)	--

#Wilcoxon rank sum test

Tocilizumab and Corticosteroids

Medications such as tocilizumab and corticosteroids were used to manage CRS and/or NE. The median $AUC_{0\text{-}28d}$ and Cmax values in subjects treated with tocilizumab for management of CRS and/or NE were 224% and 274% of those in subjects who did not receive tocilizumab for management of CRS and/or NE. The median $AUC_{0\text{-}28d}$ and Cmax values in subjects treated with corticosteroids for management of CRS or NE were 282% and 192% of those in subjects did not receive tocilizumab for management of CRS or NE. The observations correspond to the observation that higher axicel expansion levels are associated with more severe adverse events that require management with medications. Continued expansion of axicel was observed in subjects who received tocilizumab and corticosteroids.

Table 9. Axicel Pharmacokinetic Parameters and Use of Tocilizumab and Corticosteroids in Management of CRS and NE

a. Tocilizumab

	Yes (N=107)	No (N=55)	P value#
$AUC_{0\text{-}28d}$ (day*cells/μL)			
Median	325.30	144.94	0.00932**
Q1, Q3	94.95, 978.40	40.42, 465.02	
Min, Max	0.00, 16,484.28	0.004, 3,362.34	-
Cmax (cells/μL)			
Median	30.71	11.22	0.00104**
Q1, Q3	9.63, 76.04	4.20, 36.16	
Min, Max	0.04, 1,173.25	0.30, 242.74	-
Tmax (days)			
Median	8.00	8.00	-
Min, Max	8.00, 122.00	2.00, 233.00	-

b. Corticosteroids

	Yes (N=70)	No (N=92)	P value#
$AUC_{0\text{-}28d}$ (day*cells/µL)			
Median	438.59	155.43	0.00104**
Q1, Q3	120.26, 1167.96	48.36, 500.09	
Min, Max	0.004, 16,484.28	0.00, 3,362.34	-
Cmax (cells/µL)			
Median	37.60	19.59	0.00084***
Q1, Q3	10.67, 105.27	5.56, 40.42	
Min, Max	0.55, 1,173.25	0.04, 242.74	-
Tmax (days)			
Median	8.00	8.00	-
Min, Max	8.00, 233.00	2.00, 122.00	-

#Wilcoxon rank sum test

5.1.2.4 Immunogenicity

The applicant performed immunogenicity assessments 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 axicel was developed. Immunogenicity testing comprised screening enzyme-linked immunosorbent assays (ELISAs) and a confirmatory cell-based assay. The ELISA assays were first used to screen for the presence of antibodies against the murine antibody FMC63. Samples from subjects who had a positive ELISA result underwent 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 the axicel arm of Study ZUMA-7, 8 subjects tested positive in the screening ELISA assay before lymphodepletion chemotherapy. Of these 8 subjects, 7 subjects also tested positive in the screening ELISA after axicel administration. Additionally, 1 subject who had negative result before lymphodepletion tested positive after axicel infusion in the screening ELISA test. None of these subjects who tested positive in the screening ELISA tested positive in the confirmatory cell-based assays.

5.1.2.5 Replication-competent Retrovirus (RCR)

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

5.1.3 Conclusions

Following are key clinical pharmacology findings of YESCARTA (AXICEL, KTE-C19) in adults with relapsed or refractory (r/r) large B-cell lymphoma (LBCL) after first line chemoimmunotherapy:

- After the initial single dose infusion, axicel exhibited an initial rapid expansion phase followed by bi-phasic decline. After infusion on Day 0, axicel achieved peak levels in peripheral blood around Day 7 (range 2 to 233 days).

- As of data cutoff date, axicel was detected in peripheral blood in some subjects up to 24 months post-infusion, demonstrating long term persistence.

- Higher percentages of viable CAR T-cells in the final product were potentially associated with increased expansion of axicel in adult subjects with r/r LBCL.

- Higher exposure of axicel was observed in responding [complete response (CR) + partial response (PR)] subjects, compared to non-responding subjects [stable disease (SD) + progressive disease (PD)]. The median $AUC_{0\text{-}28d}$ and Cmax in responding subjects were 418% and 277% of those in nonresponding subjects, respectively.

- Higher axicel exposure were observed in subjects with Grade 2 or higher cytokine release syndrome (CRS). The median $AUC_{0\text{-}28d}$ and Cmax in subjects with Grade 2 or higher CRS were 216% and 156% of those in subjects with Grade 1 or no CRS.

- Higher axicel exposure were associated with severe neurologic events (sNE) (≥ Grade 3). The median $AUC_{0\text{-}28d}$ and Cmax in subjects with Grade 3 or higher neurologic events were 216% and 146% of those in subjects with Grade 2, Grade 1 or no neurologic events.

- Higher axicel exposure (Cmax and $AUC_{0\text{-}28d}$) was observed in subjects administered tocilizumab and/or corticosteroids for management of CRS and/or neurologic events (NE) than in subjects who did not take tocilizumab or corticosteroids for management of CRS and/or NE. The observations correspond to the observation that higher axicel expansion levels are associated to more severe adverse events that require management with medications. Axicel continued to expand in subjects who received tocilizumab and corticosteroids.

- Compared to subjects with Grade 2, Grade 1 or no CRS, substantially higher peak serum levels were observed in subjects who developed Grade 3 or higher CRS for the following biomarkers: CXCL10, ferritin, granzyme B, ICAM-1, IL-2Rα, IL-6, IL-10, IL-15, VCAM-1, GM-CSF, IL-17, and MCP-1. Higher median AUC values were observed in subjects who developed Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following biomarkers: ferritin, granzyme B, IL-2Rα, IL-6, IL-15, VCAM-1, GM-CSF, IL-17, and VEGF.

- Compared to subjects with Grade 2, Grade 1 or no neurologic events, substantially higher peak serum levels and AUC values were reported in subjects who developed Grade 3 or higher neurologic events for the following biomarkers: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IFN-γ, IL-2Rα, IL-6, IL-10, IL-15, and VCAM-1. For IL-2, and IL-5, higher peak serum levels, but not AUC values were observed in subjects with Grade 3 or higher NE compared to subjects with Grade 2, Grade 1 or no neurologic events.

- Compared to subjects who experienced Grade 2, Grade 1, or no neurologic events after infusion of axicel, subjects with Grade 3 or higher neurologic events had ≥ 2-fold higher cerebrospinal fluid (CSF) levels of CRP, ferritin, granzyme B, IFN-γ, IL-2Rα, MCP-1, and SAA.

- At Month 3 post-infusion, the percentage of subjects with B-cell aplasia increased from 42.5% (baseline) to 62.3% in the evaluable subjects. B-cell recovery was observed at Month 9 post-infusion, and continued through Month 24.

- Responding subjects with undetectable B-cell levels had higher median CAR T-cell levels than non-responding subjects with detectable B-cell levels from Month 3 to Month 24.

- Immunogenicity was assessed 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 axicel was developed. There were no positive results based on the confirmatory cell-based assay.

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