

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

BLA	125714/0
Product	Lisocabtagene Maraleucel (JCAR017, BREYANZI) cell suspension for infusion
Sponsor	Juno Therapeutics, Inc., a Celgene Company
Indication	Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies
Date Received	December 18, 2019
Reviewer	Xiaofei Wang, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation and Pharmacology/Toxicology
RPM	Olukayode Owosela Zakaria Ganiyu
Through	Tejashri Purohit-Sheth, M.D., FACAAI, CQIA Director Division of Clinical Evaluation and Pharmacology/Toxicology

Table of Contents

1	Executive Summary.....	2
2	Introduction	2
3	Summary of Important Clinical Pharmacology Findings.....	3
4	Labeling Comments.....	6
5	Recommendations	8
6	Appendix - Individual Study	9
6.1	Study #1.....	9
6.1.1	Study Design.....	9
6.1.2	Results.....	12
6.1.3	Conclusions.....	39

1 EXECUTIVE SUMMARY

Juno Therapeutics Inc. seeks approval of its JCAR017 (lisocabtagene maraleucel, BREYANZI) for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies. JCAR017 comprises autologous CD8+/CD4+ T cells transduced with a (b) (4) lentiviral vector containing an anti-CD19 chimeric antigen receptor (CAR). The proposed JCAR017 dosing regimen is a single-dose of 50 to 110 x 10⁶ CAR-positive viable T cells (consisting of CD8 and CD4 components). JCAR017 is to be administered via intravenous (IV) infusion.

The clinical pharmacology section of this biologics license application (BLA) is supported by one Phase 1 clinical study that evaluated the safety, antitumor activity, and pharmacokinetic (PK) of JCAR017 in subjects with relapsed/refractory large B-cell lymphoma after at least 2 prior therapies.

The proposed dosing regimen of JCAR017 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

JCAR017 is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies.

The JCAR017 CAR is comprised of an FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signaling is critical for initiating T-cell activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion and persistence of JCAR017. In addition, JCAR017 includes a nonfunctional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR. CAR binding to CD19 expressed on the cell surface of tumor and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines and cytotoxic killing of target cells. The JCAR017 CAR construct is delivered via a lentiviral vector.

The final product of JCAR017 is a cell suspension for infusion. JCAR017 is administered as a defined composition of CAR-positive viable T cells consisting CD8+ and CD4+ components. The CD4+ and CD8+ components of JCAR017 are provided in separate vials.

This application is supported by one human clinical study:

- An ongoing Phase 1, multicenter, multicohort, open-label study to evaluate the safety, antitumor activity, and pharmacokinetics of JCAR017 in adult subjects with refractory aggressive (R/R) non-Hodgkin Lymphoma (NHL) (Study No. 017001)

Two disease cohorts were enrolled in this study: a DLBCL cohort and mantle cell lymphoma cohort. The proposed indication in this submission is relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies. Therefore, only data from subjects with DLBCL was included in this review.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

General Cellular Kinetics/Pharmacokinetics

- JCAR017 cellular kinetics comprise lag, expansion, contraction and persistence phases in treated subjects. Following infusion, JCAR017 exhibited an initial expansion followed by a bi-exponential decline. The median time to reach peak levels in peripheral blood was 12 days post-dose. Persistence of JCAR017 transgene was observed up to 2 years.
- Compared to CD4+ EGFRt+ subset T cells, CD8+ EGFRt+ subset T cells had a higher expansion after infusion.
- Some subjects in Study 17001 received additional doses of JCAR017 in the following situations: two-dose schedule, retreatment cycles, and additional cycles.
 - In two-dose schedule, the second dose infusion (14 days after first dose) did not increase JCR017 expansion. The cellular kinetics/pharmacokinetics for two-dose schedule were similar to single-dose schedule.
 - Subjects with retreatment cycles or additional cycles treatment had substantially lower JCAR017 expansion, compared to subjects had single-dose JCAR017 treatment.

Critical Factors Impacting JCAR017 Cellular Kinetics/Pharmacokinetics

- JCAR017 expansion decreased with increase in age. Subjects < 65 years old had a 3.06-fold and 2.30-fold higher median C_{max} and AUC_{0-28d}, respectively, compared to subjects ≥ 65 years old.

- Subjects with a higher tumor burden (sum of product of perpendicular diameters (SPD) prior to LDC of $\geq 50 \text{ cm}^2$) had a 2.86-fold and 2.45-fold higher median $\text{AUC}_{0-28\text{d}}$ and C_{max} , respectively, compared to subjects with an SPD prior to LDC of $< 50 \text{ cm}^2$.
- The following product characteristics showed positive correlative relationships with JCAR017 expansion: IL-2 and $\text{TNF}\alpha$ secreted by $\text{CD4}+\text{CAR}+$ T cells, frequency of $\text{CD3}+\text{CD8}+$ CAR T cells, frequency of $\text{CCR7}+\text{CD8}+\text{CAR}+$ T cells, and $\text{CD27}+\text{CD8}+\text{CAR}+$ T cells. Higher frequency of $\text{CD28}+$ $\text{CD4}+\text{CAR}+$ T cells and apoptosis cells in $\text{CD8}+\text{CAR}+$ T cells were associated with higher T_{max} values.

Drug-Drug Interactions

- Tocilizumab and corticosteroids were used in the management of CRS and neurologic toxicities after treatment with JCAR017. Expansion of JCAR017 continued in subjects who received tocilizumab and corticosteroids after infusion of JCAR017.

Exposure-Response Relationship

- No clear dose-response of JCAR017 was observed with respect to PK (b) (4) data), PD and immunogenicity for DLBCL Cohort.
- Responders (Complete Response [CR] and Partial Response [PR]) had a 2.48-fold, 1.91-fold and 2.13-fold higher median C_{max} , $\text{AUC}_{0-28\text{d}}$, and expansion rate, respectively, compared to non-responders (Stable Disease [SD] and Progressive Disease [PD]) (b) (4) data). (b) (4) data showed similar trend with $\text{CD3}+\text{EGFRt}+$, $\text{CD4}+\text{EGFRt}+$, and $\text{CD8}+\text{EGFRt}+$ T cells. Higher expansion of $\text{CD3}+\text{EGFRt}+$, $\text{CD4}+\text{EGFRt}+$ T cells were positively associated with best overall response (BOR).
- Higher JCAR017 exposure was associated with higher incidence of any grade cytokine release syndrome (CRS) and neurologic toxicities (NT).
- (b) (4) assay data indicated that subjects with Grade ≥ 3 neurologic toxicities (NT) had substantially higher (more than 10-fold higher) median C_{max} and $\text{AUC}_{0-28\text{d}}$, and expansion rate for $\text{CD4}+\text{EGFRt}+$, respectively, compared with subjects with Grade 0-2 NT.

Pharmacodynamics

- B-cell aplasia (defined as $\text{CD19}+$ B cells comprising less than 3% of peripheral blood lymphocytes) is observed in majority of JCAR017 treated subjects for up to 1 year.
- Transient elevations of soluble biomarkers such as cytokines, chemokines were observed after infusion of JCAR017. Peak elevation of soluble biomarkers was observed within the first 14 days post JCAR017 infusion and returned to baseline levels within 28 days.
- Higher baseline levels of the following biomarkers were observed in subjects with any grade of CRS compared to subjects with no CRS: c-reactive protein (CRP), ferritin, intercellular

adhesion molecule 1 (ICAM1), IL-6, macrophage inflammatory protein 1 α (MIP1 α), serum amyloid A1 (SAA1), and TNF α .

- Higher baseline levels of the following biomarkers were observed in subjects with any grade of neurologic toxicities (NT) compared to subjects with no NT: c-reactive protein (CRP), ferritin, ICAM1, IL-6, IL-10, MIP1 α , SAA1, TNF α , and vascular cell adhesion molecule 1 (VACM1).
- Peak levels of 25 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IFN γ -induced protein 10 (IP-10), MIP1 α , transforming growth factor beta 3 (TGF β 3), and TNF α were associated with CRS.
- Peak levels of 22 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IL-10, IP-10, MIP1 α , and TNF α were associated with NT.

Immunogenicity

- Prevalence and incidence of anti-therapeutic antibody (ATA) was approximately 10%. The relationship between ATA status and JCAR017 PK was not conclusive due to small sample number of subjects who had pre-existing ATA, treatment-induced or treatment-boosted ATA.

Replication-competent Lentivirus (RCL) Testing

- No RCL has been detected in the blood in any 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

Reviewer's Comments:

Per FDA Guidance for Industry – Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016), *the CLINICAL PHARMACOLOGY section of the labeling must contain the following subsections:*

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

Please include pharmacodynamic subsection in your labeling.

12.1. Mechanism of Action

BREYANZI is a CD19-directed genetically modified autologous ~~T cellular~~ immunotherapy administered as a defined composition to reduce variability in CD8-positive and CD4-positive ~~T-cell~~ **T cell** dose. The CAR is comprised of an FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signaling is critical for initiating ~~T-cell~~ **T cell** activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion and persistence of BREYANZI.

CAR binding to CD19 expressed on the cell surface of tumor and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.

12.3. Pharmacokinetics

Reviewer's Comments:

The numbers in this section align with the clinical efficacy evaluable population who received the dose range between 50 to 110 x 10⁶ viable CAR positive T cells.

For patients who received tocilizumab and/or corticosteroids, the number of subjects should align with that in the 268 subjects of safety evaluable population.

Following infusion, BREYANZI exhibited an initial expansion followed by a bi-exponential decline. The median time of maximal expansion in peripheral blood occurred 12 days after the first infusion. BREYANZI was present in peripheral blood for up to 2 years.

Responders (N=~~175~~ 135) had a ~~4.06~~ 2.28-fold higher median C_{\max} than nonresponders (N=~~50~~ 37) (~~33,121.6~~ 35,335 vs. ~~8,160.0~~ 273,552 copies/ μ g). Responders had a ~~2.59~~ 1.76-fold higher median AUC_{0-28d} than nonresponders (~~258,584.8~~ 273,552 vs. ~~99,966.3~~ 155,240 day*copies/ μ g).

Some patients required tocilizumab and corticosteroids for the management of CRS and neurologic toxicities. Patients treated with tocilizumab (N=~~46~~ 49) had a ~~3.63~~ 4.05-fold and ~~3.69~~ 3.91-fold higher median C_{\max} and AUC_{0-28d} , respectively, compared to patients who did not receive tocilizumab (N=~~189~~ 192). Similarly, patients who received corticosteroids (N=~~50~~ 45) had a ~~3.76~~ 4.73-fold and ~~3.69~~ 3.99-fold higher median C_{\max} and AUC_{0-28d} , respectively, compared to patients who did not receive corticosteroids (N=~~188~~ 193).

Patients < 65 years old (N=142) had a 3.06-fold and 2.30-fold higher median C_{\max} and AUC_{0-28d} , respectively, compared to patients \geq 65 years old (N=96). Sex, race, ethnicity, and body weight did not show clear relationships to C_{\max} and AUC_{0-28d} .

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, multicenter, open-label study of JCAR017, CD19-targeted chimeric antigen receptor (CAR) T cells, for relapsed and refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) (Study No. 017001)

Objectives

Primary Objectives

- To evaluate the safety of JCAR017 in adult subjects with relapsed or refractory (R/R) B-cell NHL
- To assess the antitumor activity of JCAR017 (measured as overall response rate [ORR])

Secondary Objectives

- To assess the rate of complete response (CR) and durability of antitumor activity (measured as duration of response [DOR]) of JCAR017
- To estimate the progression-free survival (PFS) and overall survival (OS) of subjects treated with JCAR017
- To characterize the PK profile of JCAR017
- To assess the health-related quality of life (HRQoL) and health economics and outcomes research

Exploratory Objectives

- To assess the effect of JCAR017 on antitumor activity using Bayesian methods
- To assess immune responses to JCAR017
- To assess the pharmacodynamic effects of JCAR017
- To assess the effect of JCAR017 attributes on safety, PK, and antitumor activity
- To assess the effect of tumor and tumor microenvironment on JCAR017 PK and pharmacodynamics

Study Design

This is an ongoing Phase 1 multicenter, multicohort, open-label study to determine the safety, antitumor activity, and PK of JCAR017 in adult subjects with R/R DLBCL not otherwise specified, high-grade lymphoma (HGL) with myelocytomatosis oncogene (MYC) and B-cell lymphoma gene 2 and/or 6 (BCL2 and/or BCL6) rearrangements with DLBCL histology, primary mediastinal B-cell lymphoma (PMBCL), follicular lymphoma Grade 3B (FL3B), and Mantle Cell Lymphoma (MCL). The data cutoff date for this submission is April 12, 2019.

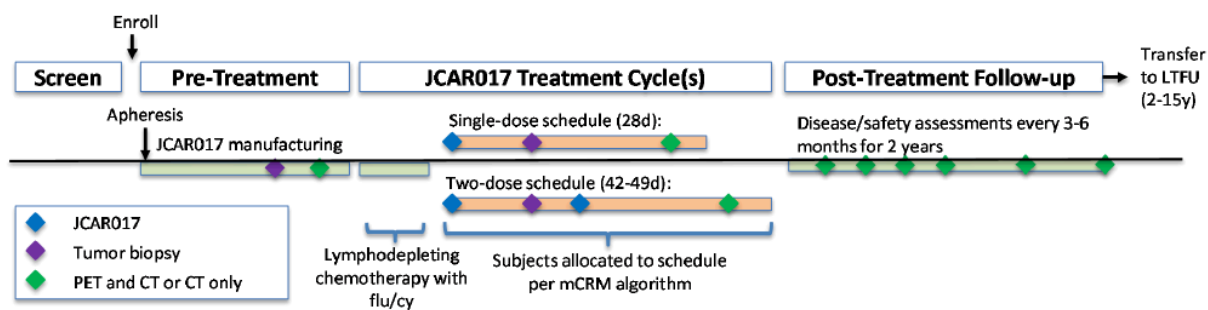
Two disease-specific cohorts were enrolled:

- DLBCL Cohort: subjects with DLBCL NOS (de novo or transformed from indolent lymphoma), HGL, PMBCL, and FL3B having received at least 2 prior lines of therapy
- MCL Cohort: subjects with MCL who received at least 1 prior line of therapy

The proposed indication in this submission is relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies. Therefore, data from subjects with DLBCL was included in this review.

As shown in Figure 1, eligible subjects underwent leukapheresis to enable JCAR017 product generation. The treatment cycle included lymphodepleting chemotherapy with fludarabine and cyclophosphamide followed by 1 (single-dose schedule) or 2 (2-dose schedule) doses of JCAR017 administered intravenously on Day 1.

Figure 1. Study Schematic



CT = computed tomography; d = days; flu/cy = fludarabine/cyclophosphamide; LTFU = long-term follow up; mCRM = modified continual reassessment method; PET = positron emission tomography

Source: Applicants Figure 1 in section 5.3.5.2. Study Report #017001, page 32.

Three dose levels (DLs) of JCAR017 were evaluated:

- 50 x 10⁶ CAR+ T cells (single and 2-dose regimen tested: DL1S (n=45) and DL1D (n=6), respectively)
- 100 x 10⁶ CAR+ T cells (single-dose regimen only: DL2S, n=176)
- 150 x 10⁶ CAR+ T cells (single-dose regimen only: DL3S, n=41).

Majority of the subjects in Study 17001 received single-doses of JCAR017. Some subjects received additional dose(s) of JCAR017 as follows:

- Two-dose schedule: subjects in this protocol-defined schedule received 2 doses of JCAR017 approximately 14 days apart as their treatment cycle. In DLBCL cycle, based on the actual

dose received, 5 subjects in Dose Level 1 and one subject in Dose Level 2 received two-dose schedule.

- Retreatment cycles: subsequent JCAR017 cycles may have been administered to a subject only if progressive disease (PD) occurred following complete response (CR) to JCAR017. In the DLBCL cohort, 11 subjects received retreatment cycles.
- Additional cycles: additional JCAR017 cycles may have been administered to a subject only if stable disease (SD) or partial response (PR) was their best overall response (BOR) after the initial response assessment. In the DLBCL cohort, 5 subjects were treated with one additional cycle and one subject was treated with two additional cycles.

For pharmacokinetic analysis, blood samples were collected at evaluation, pre-dose on Day 1, and at 3, 7, 10, 14, 21, 28, 60, 90, 180, 270, 365 days, 1.5 years and 3 years post-dose for single-dose JCAR017 regimen. In the group that received the 2-dose schedule, subjects received a 2nd JCAR017 dose 14 days after the 1st dose of JCAR017. The PK samples were collected when the dosing day transitioned to Dose #2.

The pharmacokinetic profile of JCAR017 was assessed using two validated methods:

- (b) (4) assay to detect the JCAR017 transgene
- (b) (4) to enumerate CAR T cell subsets via detection of the truncated epidermal growth factor receptor (EGFRt): ie, CD3+ EGFRt+, CD8+ EGFRt+, CD4+ EGFRt+ T cells.

PK assessments of JCAR017 were primarily based on (b) (4) measurements. PK measurements by (b) (4) assay were assessed in an exploratory and supportive manner.

Pharmacodynamic effects of JCAR017 were assessed by measuring soluble biomarker levels, B-cell enumeration, and serum immunoglobulins (Ig).

Immunogenicity was assessed by measuring anti-therapeutic antibodies (ATA) in plasma.

Replication-competent lentivirus (RCL) was assessed using (b) (4) to detect viral vector envelop sequences in blood.

6.1.2 Results

6.1.2.1 Cellular Kinetics/Pharmacokinetics

6.1.2.1.1 General Cellular Kinetic/Pharmacokinetic Characteristics for All Treated Subjects

In the DLBCL cohort of Study 17001, a total of 268 subjects received JCAR017 treatment and pharmacokinetic profiles were obtained for all 268 subjects.

Single-dose Regimen

(b) (4) PK Analysis

As shown in Table 1 and Figure 2, following infusion, JCAR017 exhibited an initial expansion followed by a bi-exponential decline. The median time to reach peak expansion (T_{max}) was 14, 11, and 10 days after the first dose for DL1S, DL2S and DL3S, respectively. The median C_{max} and AUC_{0-28d} values were similar across all three dose levels with a single-dose regimen. The median expansion rates were 1239.8 copies/μg DNA/day (range: 2.0, 26124.0 copies/μg DNA/day), 2400.7 copies/μg DNA/day (range: 20.0, 37409.0 copies/μg DNA/day), and 2231.7 copies/μg DNA/day (range: 75.0, 47470.0 copies/μg DNA/day) for DL1S, DL2S, and DL3S groups, respectively. The expansion rate of JCAR017 in DL1S group was lower than DL2S and DL3 groups.

For all three dose levels in the DLBCL cohort, after the 1st dose JCAR017 administration, the median T_{max} was 12 days, median C_{max} and AUC_{0-28d} were 23964 copies/μg DNA and 214283 day*copies/ μg DNA, respectively. The persistence of JCAR017 in peripheral blood was up to 2 years (Day 730) in the DLBCL cohort with single-dose schedule.

Table 1. Summary of JCAR017 Transgene Pharmacokinetic Parameters After Single-Dose of JCAR017 (DLBCL Cohort, (b) (4) Analysis Set)

Parameter Statistic	DL1S N = 44	DL2S N = 176	DL3S N = 41	DL1S + DL2S + DL3S N = 261
n ^b	40	166	32	238
C _{max} (copies/μg)				
Median	20958.2	25098.5	23548.8	23963.7
Q1, Q3	5634.7, 71868.6	9806.3, 79118.5	6374.9, 71267.3	8159.3, 78748.2
t _{max} (day)				
Median	14.0	11.0	10.0	12.0
Q1, Q3	12.0, 19.5	10.0, 14.0	7.5, 14.0	10.0, 15.0
AUC ₀₋₂₈ (day*copies/μg)				
Median	186994.0	229062.6	185393.9	214283.0
Q1, Q3	41717.3, 510264.9	96750.8, 689751.7	54491.0, 849879.3	77281.7, 689751.7

AUC₀₋₂₈ = area under the concentration-time curve through 28 days after infusion (ie, from Day 1 to Day 29); C_{max} = maximum observed concentration; DL1D = Dose Level 1, 2-dose regimen; DL1S = Dose Level 1, single-dose regimen; DL2S = Dose Level 2, single-dose regimen; DL3S = Dose Level 3, single-dose regimen; DLBCL = diffuse large B-cell lymphoma;

N = number of subjects in the population; n = number of subjects analyzed; Q1, Q3 = first and third quartiles;

(b) (4)

t_{max} = time to maximum observed concentration

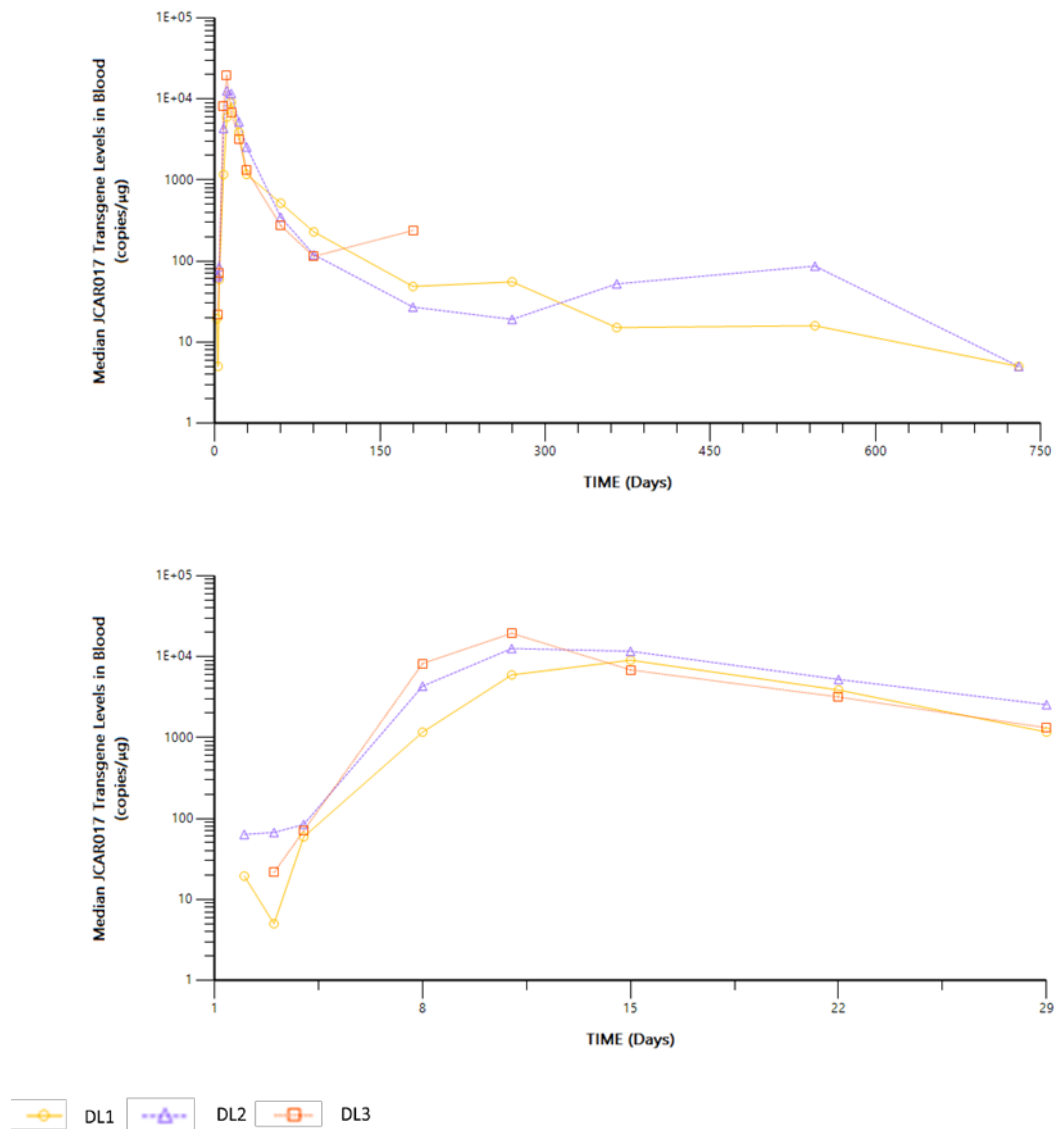
Note: The (b) (4) K Analysis Set includes subjects in the JCAR017-treated Analysis Set who have both baseline and on-study PK measurements as assessed by (b) (4)

^a PK parameters for DL1D were based on data after the second infusion.

^b Number of subjects who had PK parameters. Noncompartmental PK parameters were calculated for subjects who had PK measurement on Day 29 or later.

Source: Applicant. Table 7 in section 5.3.4.2. Clinical Pharmacology Study Report #017001, page 35.

Figure 2. Cellular Kinetic/Pharmacokinetic Profiles of JCAR017 after Single-Dose Administration (DLBCL Cohort, (b) (4) Analysis Set)



(b) (4) PK Analysis

PK/cellular kinetic parameters of CD3+ EGFRt+, CD8+ EGFRt+, CD4+ EGFRt+ T cells measured by (b) (4) assay are summarized in Table 2. The Tmax values for the (b) (4) analysis set were similar to the Tmax values of (b) (4) set for all 3 dose levels. The median expansion rate of CD3+ EGFRt+ T cells were 2.0, 4.6, and 7.7 cells/μL/day for DL1S, DL2S, and DL3S groups, respectively. JCAR017 expansion (Cmax, AUC0-28d, and expansion rate) in DL1 were lower than DL2 and DL3. JCAR017 expansion were similar between DL2 and DL3.

The median expansion rate of CD4+ EGFRt+ T cells were 0.4, 0.7, and 0.6 cells/μL/day for DL1S, DL2S, and DL3S groups, respectively. The median expansion rate of CD8+ EGFRt+ T cells were 1.1, 3.4 and 5.5 cells/μL/day for DL1S, DL2S, and DL3S groups, respectively. The expansion of the CD8+ EGFRt+ T cell subset was substantially higher than the CD4+ EGFRt+ T cell subset: 3.1 (range: 0.0, 336.0) cells/μL/day vs. 0.6 (0.0, 144.0) cells/μL/day (Figure 3).

Table 2. Summary of JCAR017 Transgene Pharmacokinetic Parameters After Single-Dose of JCAR017 (DLBCL Cohort, (b) (4) Analysis Set)

Parameter Statistic	DL1S N = 45	DL2S N = 176	DL3S N = 41	DL1S + DL2S + DL3S N = 262
n ^b	41	168	39	248
CD3+ EGFRt+:				
C _{max} (cells/μL)				
Median	28.0	58.2	66.0	56.4
Q1, Q3	8.0, 116.4	16.2, 176.7	11.1, 203.6	13.0, 166.3
t _{max} (day)				
Median	14.0	11.5	10.0	13.0
Q1, Q3	10.0, 15.0	10.0, 15.0	9.0, 14.0	10.0, 15.0
AUC ₀₋₂₈ (day*cells/μL)				
Median	271.1	526.3	540.3	452.0
Q1, Q3	62.1, 644.3	138.5, 1375.2	120.9, 1508.1	110.5, 1343.4
CD4+ EGFRt+:				
C _{max} (cells/μL)				
Median	5.1	7.7	5.8	6.9
Q1, Q3	1.8, 28.6	2.1, 23.0	1.7, 20.5	1.9, 23.0
t _{max} (day)				
Median	14.0	11.0	10.0	11.0
Q1, Q3	10.0, 16.0	10.0, 14.0	9.0, 14.0	10.0, 14.5
AUC ₀₋₂₈ (day*cells/μL)				
Median	39.3	60.9	48.0	52.6
Q1, Q3	14.6, 190.6	20.0, 185.5	18.4, 138.5	18.0, 184.0

CD8+ EGFRt+:				
C_{max} (cells/ μ L)				
Median	16.9	45.8	54.3	41.7
Q1, Q3	2.7, 93.1	11.7, 151.1	9.4, 200.4	9.2, 142.3
t_{max} (day)				
Median	14.0	11.0	11.0	12.0
Q1, Q3	10.0, 15.0	10.0, 15.0	9.0, 14.0	10.0, 15.0
AUC_{0-28} (day*cells/ μ L)				
Median	153.4	419.8	413.7	339.6
Q1, Q3	16.6, 391.9	111.7, 1075.7	110.9, 1229.5	80.1, 1012.8

AUC_{0-28} = area under the concentration-time curve through 28 days after infusion (ie, from Day 1 to Day 29); C_{max} = maximum observed concentration; DL1D = Dose Level 1, 2-dose regimen; DL1S = Dose Level 1, single-dose regimen; DL2S = Dose Level 2, single-dose regimen; DL3S = Dose Level 3, single-dose regimen; DLBCL = diffuse large B-cell lymphoma; EGFRt = truncated epidermal growth factor receptor; N = number of subjects in the population; n = number of subjects analyzed; PK = pharmacokinetics; Q1, Q3 = first and third quartiles; t_{max} = time to maximum observed concentration

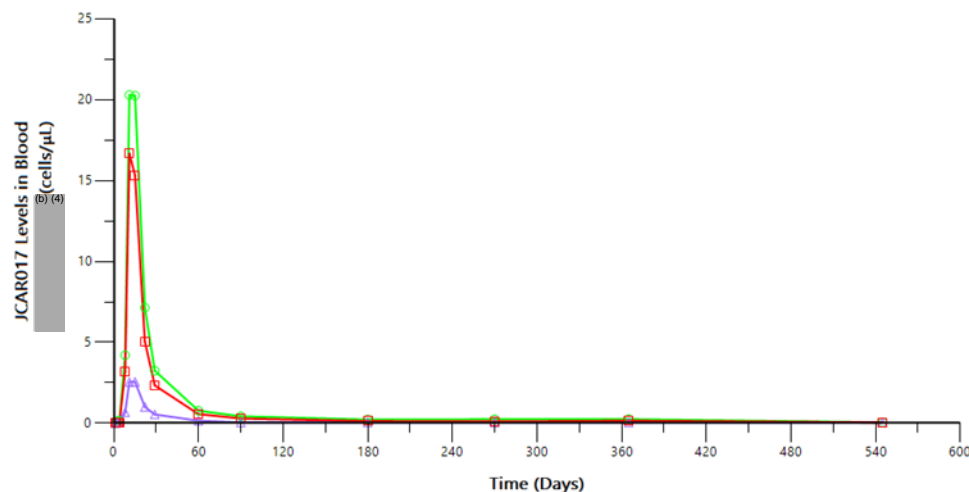
Note: The (b) (4) PK Analysis Set includes subjects in the JCAR017-treated Analysis Set who have both baseline and on-study PK measurements as assessed by (b) (4)

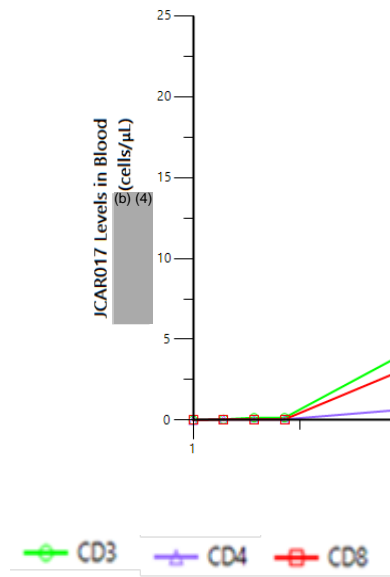
^a PK parameters for DL1D were based on data after the second infusion.

^b Number of subjects who had PK parameters. Noncompartmental PK parameters were calculated for subjects who had PK measurement on Day 29 or later.

Source: Applicant. Table 8 in section 5.3.4.2. Clinical Pharmacology Study Report #017001, page 37-38.

Figure 3. Cellular Kinetic/Pharmacokinetic Profiles of JCAR017 after Single-Dose Administration (DLBCL Cohort, (b) (4) Analysis Set)

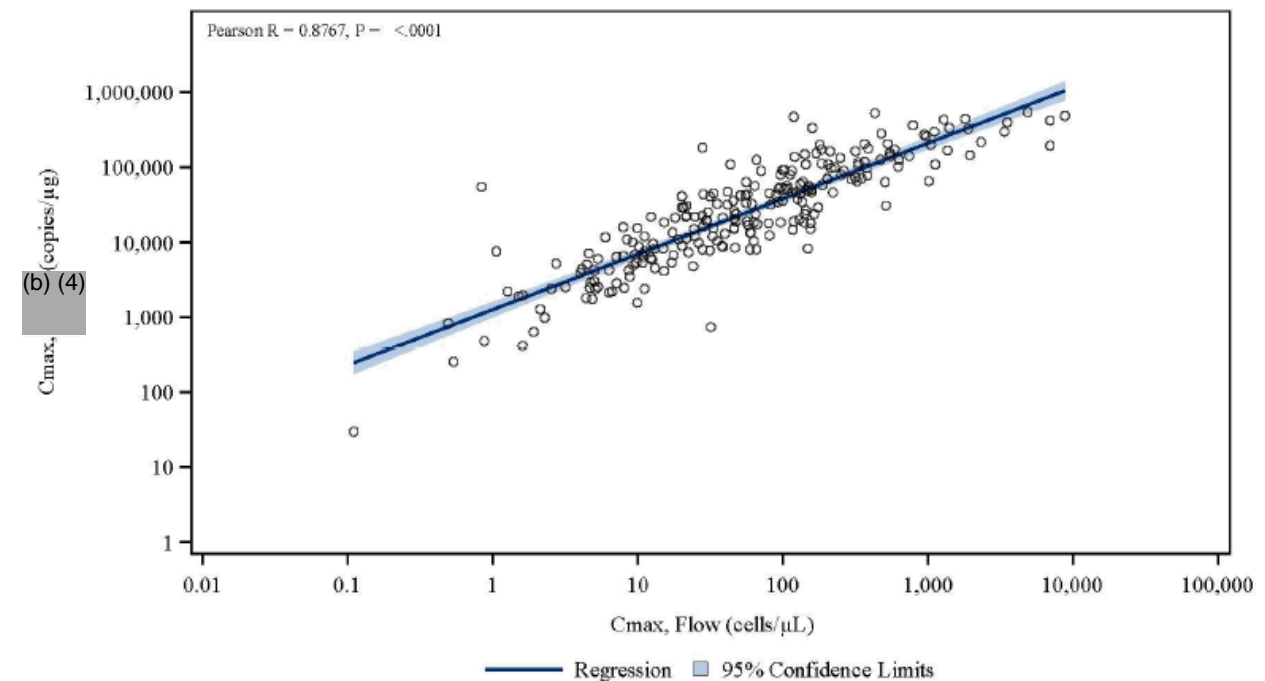


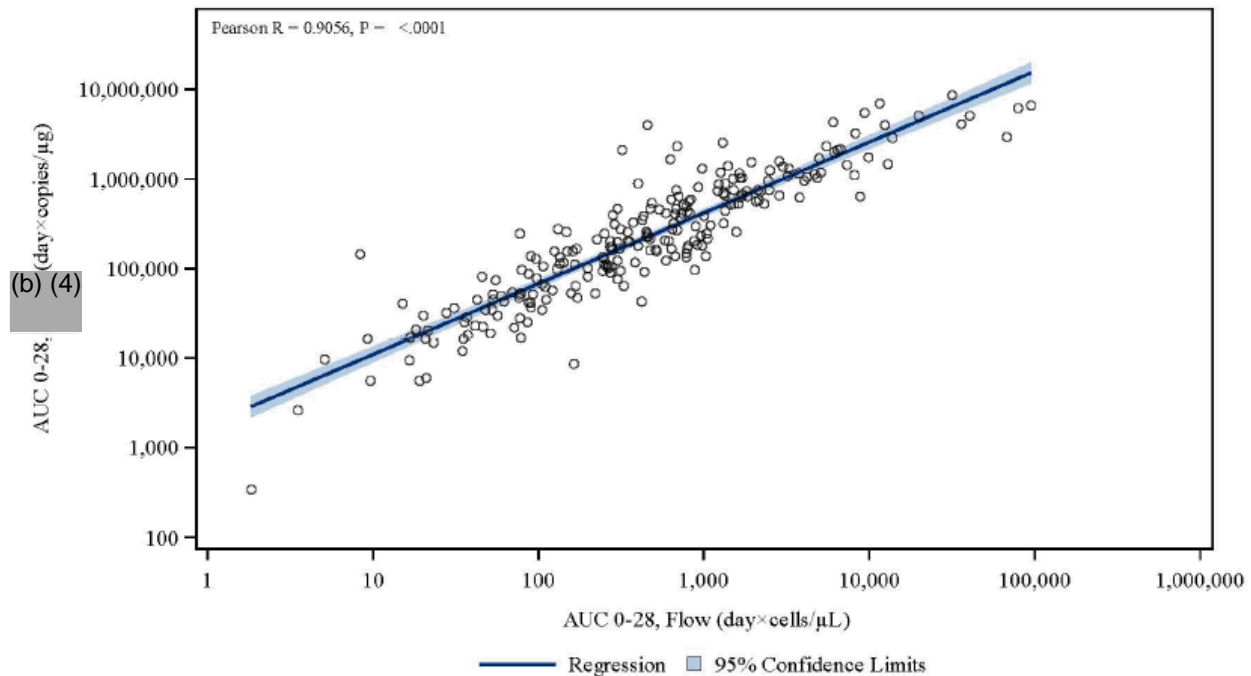


Correlation between PK Parameters by (b) (4) Assay and PK Parameters by (b) (4) Assay

The relationship between (b) (4) and (b) (4) PK parameters appeared to be linear (Figure 4).

Figure 4. Correlation of Transgene PK Parameters between (b) (4) Measurements (DLBCL Cohort, Single-dose Schedule)





Source: Applicant. Figure 2 & 3 in section 5.3.4.2. Clinical Pharmacology Study Report #017001, page 39-40.

Cellular Kinetics/Pharmacokinetics of Additional Doses of JCAR017

As stated in the study design section, some subjects received more than one dose of JCAR017 in Study 17001 via one of the following scenarios: two-dose schedule, retreatment cycles and additional cycles.

Two-Dose Schedule

As shown in Table 3, in the two-dose schedule, the first dose showed similar JCAR017 expansion as a single-dose JCAR017 infusion. The second dose did not further increase JCAR017 expansion. The PK parameters for the two-dose schedule were calculated from administration of first dose on Day1. The PK parameters for the two-dose schedule were comparable to the PK parameters for the single-dose schedule. One subject in the DL1D group received the Dose Level 2 amount of JCAR017 with the two-dose schedule. The PK parameters for this subject were within the range of PK parameters for DL2S single-dose group.

Table 3. Comparison of JCAR017 PK Parameters Between Single-dose Schedule and Two-Dose Schedule (DLBCL Cohort)

PK Parameters (Median (range))	Single-dose Schedule	Two-Dose Schedule
Dose Level 1		
N	40	5
C_{max} (copies/μg DNA)	20958.2 (29.0, 539903.0)	28869.9 (17573.6, 59937.5)

Tmax (days)	14.0 (7.0, 112.0)	11.0 (8.0, 18.0)
AUC_{0-28d} (day* copies/μg DNA)	186994.0 (344.0, 8539093.0)	269031.6 (172359.1, 723356.2)
Expansion Rate (copies/μg DNA/day)	1239.8 (2.0, 26124.0)	3608.7 (976.3, 4658.5)

Reviewer's Comments:

Per the applicant, the JCAR017 PK assessment was calculated using PK measurements following the second dose. This reviewer does not agree with the applicant's method. The PK assessment should include PK measurements following the first dose of JCAR017 as well. Therefore, the reviewer's PK assessment for two-dose schedule included PK measurements after the administration of the first dose.

Retreatment Cycles

Compared to first treatment of JCAR017, JCAR017 expansion was substantially lower after retreatment (Table 4) with slower expansion rate and shorter length of expansion phase. The median dose interval between the first treatment and retreatment was 250 days (range: 96 – 567 days).

Table 4. Comparison of JCAR017 PK Parameters Between First Treatment and Retreatment (DLBCL Cohort)

PK Parameters (Median (range))	First Treatment	Retreatment
N	11	11
Cmax (copies/μg DNA)	89868.3 (483.4, 479395.7)	852.1 (5, 10323.8)
Tmax (days)	11.0 (7.0, 29.0)	3.0 (0.0, 21.0)
AUC_{0-28d} (day* copies/μg DNA)	623785.9 (5536.1, 6219793.1)	3370.7 (139, 41712.5)
Expansion Rate (copies/μg DNA/day)	8986.8 (40.3, 17964.2)	302.9 (41.3, 2296.5)

Additional Cycles

In Study 17001, 6 subjects received a second cycle treatment of JCAR017. The median dose interval between first and second cycle was 69.5 days (range: 63 – 163 days). One subject received a third cycle treatment of JAR017 49 days after the second cycle. Compared to first cycle treatment of JCAR017, JCAR017 expansion was substantially lower after additional treatment cycles. (Table 5).

Table 5. Comparison of JCAR017 PK Parameters Between First Cycle and Second Cycle (DLBCL Cohort)

PK Parameters (Median (range))	First Cycle	Second Cycle
N	6	6
C _{max} (copies/μg DNA)	32409.9 (1268.4, 16191.0)	399.4 (40.7, 35234.5)
T _{max} (days)	14.0 (10.0, 23.0)	4.5 (1.0, 36.0)
AUC _{0-28d} (day* copies/μg DNA)	234622.2 (16385.1, 863283.1)	1140.4 (185.9, 260387.3)
Expansion Rate (copies/μg DNA/day)	2341.3 (55.1, 16195.1)	130.9 (1.1, 1761.7)

Below Table showed JCAR017 PK parameters of the subject who had two additional cycles.

Table 6. JCAR017 PK Parameters of the Subject Received Two Additional Cycles

PK Parameters	First Cycle	Second Cycle	Third Cycle
C _{max} (copies/μg DNA)	41093.6	35234.5	7840.9
T _{max} (days)	13.0	20.0	4.0
AUC _{0-28d} (day* copies/μg DNA)	242072.4	260387.3	94518.1
Expansion Rate (copies/μg DNA/day)	3161.0	1761.7	1960.2

Factors Impacting JCAR017 Cellular Kinetics/Pharmacokinetics

Various baseline and demographic characteristics, disease characteristics, manufacturing process, and the use of tocilizumab and/or corticosteroids for the treatment of cytokine release syndrome (CRS) or neurologic toxicities (NT) were evaluated for their relationship to JCAR017 expansion (C_{max}, AUC_{0-28d}, and T_{max}) in the DLBCL cohort with the single-dose schedule. Among these factors, age and sum of product of perpendicular diameters (SPD) prior to lymphodepleting chemotherapy were observed to be associated with JCAR017 expansion. Multivariate PK analysis also showed the relationship between age, SPD and JCAR017 expansion. Please refer to pharmacometric review for details.

Baseline and Demographic Characteristics

The following baseline demographic were evaluated with respect to JCAR017 expansion: age, sex, race, ethnicity, body weight, body mass index, serum creatine, ALT, AST, and total bilirubin.

Age

Comparison of JCAR PK parameters among different age groups is shown in Table 7. With the increased age, JCAR017 expansion decreased. Subjects < 65 years old (n=142) had a 3.06-fold and 2.30-fold higher median Cmax (p<0.0001) and AUC_{0-28d} (p<0.0001), respectively, compared to subjects ≥ 65 years old (n=96).

Table 7. Analysis of JCAR017 Expansion by Age (DLBCL Cohort, Single-dose)

	N	AUC _{0-28d} (days*copies/μg) Median (min, max)	Cmax (copies/μg) Median (min, max)	Tmax (day) Median (min, max)
< 65 years	142	312636 (2602-8539093)	43440 (257-539903)	13.0 (6.0-41.0)
≥ 65 years	96	135843 (344-5144642)	14195 (29-443878)	11.0 (7.0-112.0)
< 75 years	215	242072 (344-8539093)	29474 (29-539903)	12.0 (6.0 – 112.0))
≥ 75 years	23	111936 (9475-1724546)	11856 (984-203048)	10.0 (7.0 – 21.0)
< 40 years	23	689751 (6055-8539093)	56950 (643-539903)	14.0 (6.0-29.0)
≥ 40 to < 65 years	119	256953 (2602-7002122)	34410 (257-479396)	13.0 (6.0-41.0)
≥ 65 years	96	135843 (344-5144642)	14195 (29-443878)	11.0 (7.0-112.0)

Sex

In Study 17001, 154 subjects (65%) were male and 84 (35%) were female. The median (range) AUC_{0-28d} of JCAR017 were 204218 days*copies/μg DNA (344 – 8539093 days*copies/μg DNA) and 255836 days*copies/μg DNA (8573 – 5068457 days* copies/μg DNA) for male and female subjects respectively. The median (range) Cmax of JCAR017 was 23836 copies/μg DNA (29 – 539903 copies/μg DNA) and 29868 copies/μg DNA (748 – 467249 copies/μg DNA) for males and females, respectively. The median values of Tmax were 13.0 and 10.0 days for males and females, respectively. Due to the high variability of PK parameters and small sample size, no statistically significant impact of sex on PK parameters (AUC_{0-28d} and Cmax) was noted.

Race

About 89.5% of the populations studied in Study 17001 were white subjects. Therefore, comparisons across race or ethnicity were not possible.

Disease Characteristics

The following disease characteristics were assessed for potential association with JCAR017 expansion: lactate dehydrogenase (LDH) prior to lymphodepleting chemotherapy (LDC), sum of product of perpendicular diameters (SPD) prior to LDC, baseline CRP, prior HSCT status, prior response status, prior chemo-response status, CNS disease status, and T cell of origin.

Significant differences in JCAR017 expansion were observed between subjects with SPD prior to LDC of $\geq 50 \text{ cm}^2$ and subjects with an SPD prior to LDC of $< 50 \text{ cm}^2$.

Tumor Burden – Sum of Product of Perpendicular Diameters (SPD) Per IRC Prior to LDC

As shown in Table 8, higher tumor burden was associated with increased JCAR017 expansion.

Subjects with an SPD prior to LDC of $\geq 50 \text{ cm}^2$ had a 2.86-fold and 2.45-fold higher median $\text{AUC}_{0-28\text{d}}$ and Cmax , respectively, compared to subjects with an SPD prior to LDC of $< 50 \text{ cm}^2$.

Table 8. Analysis of JCAR017 Expansion by Tumor Burden (DLBCL Cohort, Single-dose)

SPD	N	$\text{AUC}_{0-28\text{d}}$ (days*copies/ μg) Median (min, max)	Cmax (copies/ μg) Median (min, max)	Tmax (day) Median (min, max)
$\geq 50 \text{ cm}^2$	59	523567 (5522-7002122)	53399 (423-479396)	14.0 (7.0-29.0)
$< 50 \text{ cm}^2$	167	183268 (344-8539093)	21760 (29-539903)	11.0 (6.0-112.0)
P values*		0.0011	0.0114	0.0004

*Wilcoxon rank sum test

Cellular Kinetics/Pharmacokinetics of JCAR017 in Subjects Who Used Tocilizumab and Corticosteroids

Tocilizumab and corticosteroids were used in the management of cytokine release syndrome (CRS) and neurologic toxicities (NT) in Study 17001. Subjects treated with tocilizumab (n=49) had a 2.69-fold, 2.63-fold, and 2.63-fold higher median JCAR017 $\text{AUC}_{0-28\text{d}}$, Cmax , and expansion rate, respectively, compared to subjects who did not receive tocilizumab (n=189) (Table 9). Similarly, subjects that received corticosteroids (n=50) had a 2.69-fold, 2.76-fold, and 2.17-fold higher median JCAR017 $\text{AUC}_{0-28\text{d}}$, Cmax , and expansion rate, respectively, compared to patients who did not receive corticosteroids (n=188) (Table 10). JCAR017 continued its expansion after administration of tocilizumab and /or corticosteroids.

Table 9 Analysis of JCAR017 Expansion by Tocilizumab Taken (DLBCL Cohort, Single-dose)

	Tocilizumab Taken Post JCAR017 Infusion	
	Yes (N=49)	No (N=189)
AUC _{0-28d} (day*copies/μg DNA)		
Median	613890.2	166171.6
Min, Max	2602.2, 8539093.1	344.0, 6219793.1
Cmax (copies/μg DNA)		
Median	71017.7	19539.8
Min, Max	256.9, 539903.0	29.3, 479395.7
Tmax (day)		
Median (Q1, Q3)	10.0	13.0
Min, Max	6.0, 29.0	6.0, 112.0
Expansion Rate (copies/μg DNA/day)		
Median	6660.6	1834.9
Min, Max	19.8, 37634.7	2.3, 47470.4

Table 10. Analysis of JCAR017 Expansion by Corticosteroid Administration (DLBCL Cohort, Single-dose)

	Corticosteroids Administration Post JCAR017 Infusion	
	Yes (N=50)	No (N=188)
AUC _{0-28d} (day*copies/μg DNA)		
Median	631801.1	171286.3
Min, Max	15005.2, 8539093.1	344.0, 5144464.2
Cmax (copies/μg DNA)		
Median (78557.0	20890.4
Min, Max	3024.5, 539903.0	29.3, 467249.1
Tmax (day)		
Median (Q1, Q3)	11.5	12.0
Min, Max	6.0, 30.0	6.0, 112.0
Expansion Rate (copies/μg DNA/day)		
Median	5881.2	1853.1
Min, Max	302.4, 37408.5	2.3, 47470.4

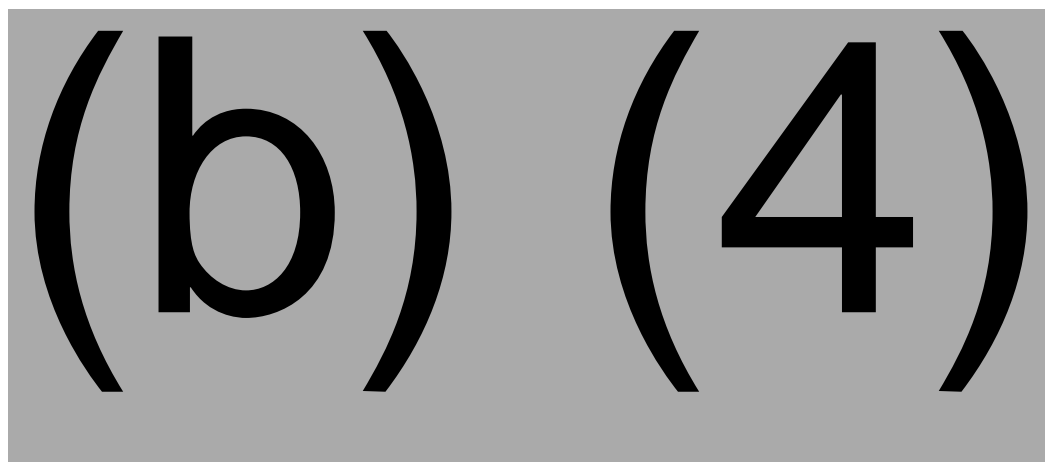
CMC Factors – Manufacturing Procedure and Product Characteristics

Exploratory analysis was conducted for possible relationships of JCAR017 PK and CMC factors, including manufacturing process version and product characteristics.

Manufacturing Process

In Study 17001, JCAR017 from ^{(b) (4)} different manufacturing process versions was used (Table 11).

Table 11. Number of Subjects Treated at DL1S and DL2S by Manufacturing Process Version and Vector Manufacturing Site (DLBCL Cohort)



Multivariable analysis was conducted with clinical and PK data from subjects administered DL1S and DL2S JCAR017 from (b) (4) manufacturing processes. DL3S data was excluded due to short follow-up time. JCAR017 from (b) (4) had shorter median Tmax (11.0 days, range: 6.0-29.0 days) than JCAR017 from (b) (4) (14.0 days, range: 7.0-41.0 days). Subjects dosed with (b) (4) process at (b) (4) showed relatively lower median Cmax and AUC_{0-28d} compared to subjects dosed with (b) (4) process versions or (b) (4) process version at (b) (4) site. However, due to considerable inter-subject variability in PK parameters, no definitive differences in PK parameters and persistence of JCAR017 were identified across different manufacturing process versions or manufacturing sites.

Product Characteristics

The following final product quality characteristics were evaluated: CD4:CD8 ratio, cell viability, viable cell concentration, IFN γ secretion, vector copy number, memory T cell composition (T cell subsets), antigen-specific cytokine production, and percentage of active caspase 3+ CAR+ T cells.

The CD4:CD8 ratio was clustered within the range of 0.7-1.30 in approximately 94% of subjects in the DLBCL cohort single-dose schedule. No clear relationship between JCAR017 CD4:CD8 ratio and PK parameters was observed.

The following potential positive correlative relationships with JCAR017 PK product characteristics and PK parameters were suggested:

For CD4+ CAR+ T cells:

- IL-2 secreted by CD4+ CAR+ T cells and higher Cmax (p=0.0242), ρ =+0.21)

- TNF α secretion by CD4+ CAR + T cells and higher Cmax (p=0.0462), ρ =+0.18)
- Frequency of CD28+ CD4+CAR+ T cells and Tmax (p=0.0335, ρ =+0.20)

For CD8+ CAR+ T cells:

- Frequency of CD3+CD8+CAR+ T cells and AUC_{0-28d} (p=0.0335, ρ =+0.20) and Cmax (p=0.0382, ρ =+0.20)
- Frequency of CCR7+CD8+CAR+ T cells and AUC_{0-28d} (p=0.0325, ρ =+0.20) and Cmax (p=0.0196, ρ =+0.22)
- Frequency of CD27+CD8+CAR+ T cells and Cmax (p=0.0414, ρ =+0.19)
- Frequency of apoptosis cells in CD8+CAR+ T cells and Tmax (p=0.0063, ρ =+0.25)

6.1.2.2 Exposure-Response Relationship

The exposure-response relationship for JCAR017 was performed on data from the single-dose schedule in the DLBCL cohort.

Exposure-Response for Efficacy

(b) (4) Assay Data

The relationship between JCAR017 exposure and efficacy was conducted based on the results from the clinical reviewer's efficacy analysis. As shown in Table 12, responders [complete response (CR) or partial response (PR)] (N=135) had a 2.28-fold, 1.76-fold and 2.13-fold higher median C_{max}, AUC_{0-28d}, and expansion rate, compared to nonresponders [non-response (NR)] (N=37). The median Tmax values were 11.0 days and 14.0 days for responding and non-responding subjects, respectively. Logistic analysis indicated that JCAR017 peak levels and expansion rate were positively associated with subjects' responses (Table 13).

Table 12. Comparison of JCAR017 Pharmacokinetic Parameters between Responding and Non-Responding Subjects (DLBCL Cohort, Single-Dose Schedule, Efficacy Analysis Set, (b) (4) Assay)

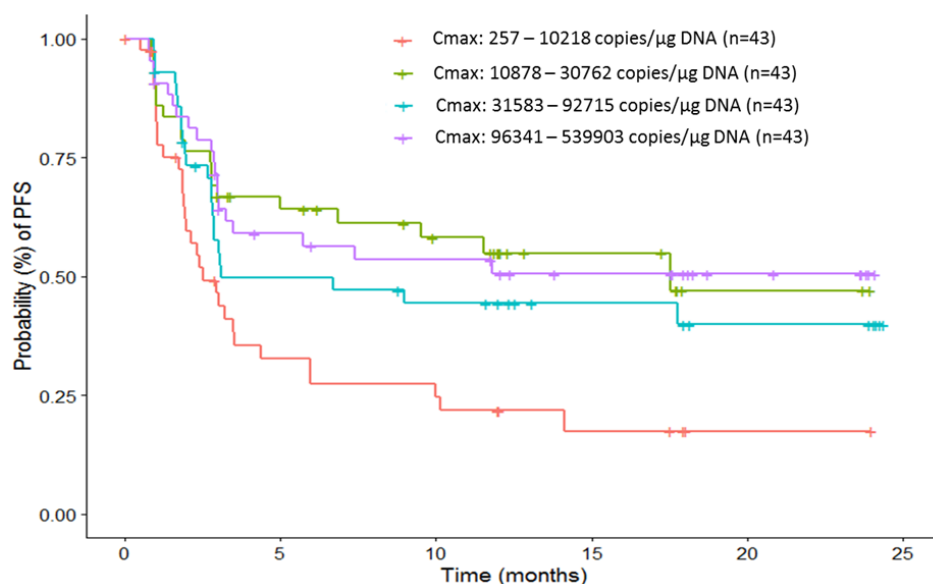
Parameters (Unit)	Unit	Responding Subjects N=135	Non-Responding Subjects N=37	P value
Cmax [median, (min, max)]	copies/ μ g DNA	35335.0 (256.9, 539903.0)	15526.9 (422.5, 528736.9)	0.0233
Tmax [median, (min, max)]	day	11.0 (6.0, 30.0)	14.0 (6.0, 41.0)	0.0697
AUC _{0-28d} [median, (min, max)]	days*copies/ μ g DNA	273552 (2602.0, 8539093.0)	143460.5 (5522.0, 6646582.0)	0.0467
Expansion Rate [median, (min, max)]	copies/ μ g DNA/day	3157.1 (19.8, 32396.9)	1477.6 (26.4, 37408.5)	0.0089

Table 13. Logistic Regression Analysis Between JCAR017 Expansion and Responses (DLBCL Cohort, Single-Dose Schedule, Efficacy Analysis Set, (b) (4) Assay)

Log Cmax			
	Odds Ratio	p value	95% CI
Intercept	0.2450	0.2635	0.0201 – 2.9002
LogCmax	1.8494	0.0325	1.0592 – 3.2982
Log AUC _{0-28d}			
	Odds Ratio	p value	95% CI
Intercept	0.2191	0.3132	0.0110 – 4.1897
LogAUC _{0-28d}	1.6914	0.0628	0.9789 – 2.9838
Log Expansion Rate			
	Odds Ratio	p value	95% CI
Intercept	0.3103	0.2189	0.0465 – 2.0120
Log Expansion Rate	2.1137	0.0098	1.2070 – 3.7970

Correlation between JCAR017 expansion (Cmax, AUC_{0-28d} and expansion rate) and progression free survival (PFS) was assessed by Kaplan-Meier survival analysis. As shown in Figure 5, JCAR017 expansion in the lowest quantile range was associated with lower probability of PFS. However, there was no evident difference for JCAR017 expansion in the upper 3 quantile ranges regarding PFS. Cox proportional hazard regression also suggested that higher JCAR017 expansion was associated with longer PFS (Table 14).

Figure 5. Kaplan-Meier plot of progression free survival (PFS) by JCAR017 Expansion Quantile Groups (Efficacy Analysis Set, (b) (4) Assay)



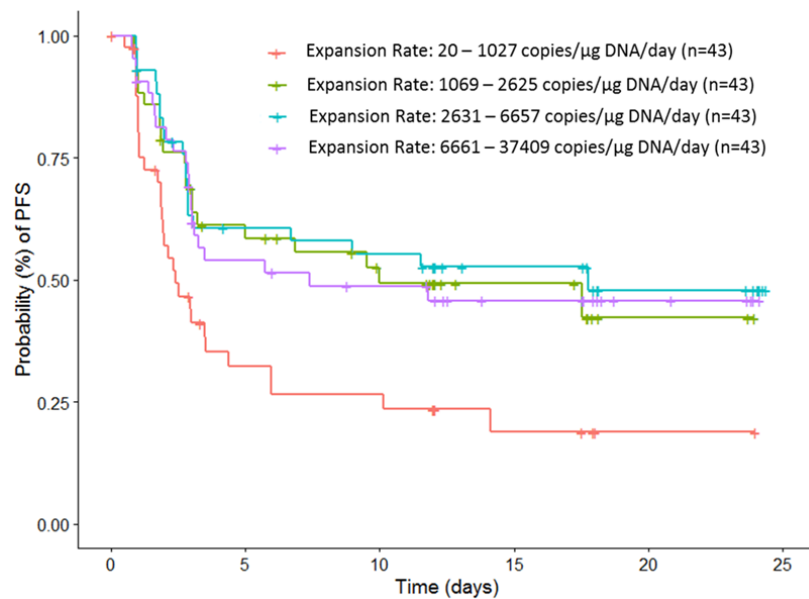
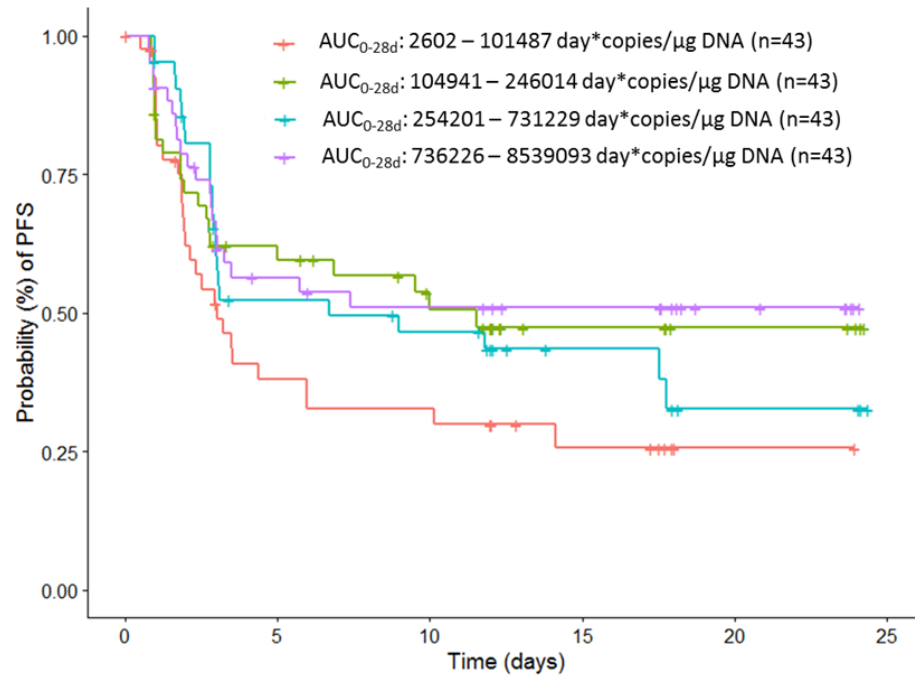


Table 14. Cox Proportional Hazard Analysis Between JCAR017 Expansion and Progress Free Survival (PFS) (DLBCL Cohort, Single-Dose Schedule, Efficacy Analysis Set, (b) (4) Assay)

	Hazard Ratio	95% CI for Hazard Ratio	p value
LogCmax	0.6654	0.4794 – 0.9236	0.0149
LogAUC _{0-28d}	0.7064	0.5099 – 0.9788	0.0367
LogExpansionRate	0.6182	0.4474 – 0.8542	0.0036

(b) (4) *Assay Data*

As indicated in Table 15, the analysis of relationship between JCAR017 exposure and efficacy using (b) (4) assay data showed similar results as the analysis results from (b) (4) data. Responding subjects had higher expansion in CD3+EGFRt+, CD4+EGFRt+, and CD8+EGFRt+ T cells subsets. Higher expansion of CD3+EGFRt+, and CD4+EGFRt+ T cells were positively associated with best overall response (BOR). Higher expansion in CD3+EGFRt+, CD4+EGFRt+, and CD8+EGFRt+ T cells were associated with longer progress free survival (PFS).

Table 15. Summary of Correlative Analysis Between JCAR017 PK and Efficacy Responses (DLBCL Cohort, Single-dose Schedule, (b) (4) Analysis)

	CD3+ EGFRt+			CD4+ EGFRt+			CD8+ EGFRt+		
	Cmax	AUC _{28d}	ExpRate	Cmax	AUC _{28d}	ExpRate	Cmax	AUC _{28d}	ExpRate
Responders vs. nonresponders, median fold ratio P value*	3.33-fold P=0.0213	2.37-fold P=0.0217	2.60-fold P= 0.0078	1.97-fold P=0.0091	2.17-fold P=0.0073	3.30-fold P=0.0027	2.81-fold P=0.0443	2.14-fold P=0.0493	3.15-fold P=0.0390
	LogCmax	LogAUC _{28d}	LogExpRate	LogCmax	LogAUC _{28d}	LogExpRate	LogCmax	LogAUC _{28d}	LogExpRate
Odds Ratio (95% CI) P value	1.6786 (1.0532-2.7470) P=0.0332	1.6883 (1.0475-2.8037) P=0.0361	1.7520 (1.0945-2.8749) P=0.0220	1.9072 (1.1685-3.2395) P=0.0126	1.9899 (1.1858-3.5083) P=0.0125	2.0555 (1.2449-3.5258) P=0.0063	1.4989 (0.9647-2.3758) P=0.0768	1.5074 (0.9638-2.4097) P=0.0776	1.4760 (0.9504-2.3277) P=0.0866
PFS Hazard Ratio (95% CI), P value	0.6864 (0.5211 – 0.904) P=0.0074	0.7016 (0.5302, 0.9286) P=0.0132	0.6813 (0.5212 – 0.8905) P=0.0050	0.7327 (0.5596 – 0.9594) 0.0237	0.7616 (0.5757 – 1.007) P=0.0563	0.6695 (0.5073 – 0.8835) P=0.0046	0.7104 (0.5486 – 0.9201) P=0.0096	0.7131 (0.5478 – 0.9283) P=0.0120	0.7236 (0.5661 – 0.925) P=0.0098

*Wilcoxon rank sum test

Exposure-Response for Safety

Exposure and Cytokine Release Syndrome (CRS)

Subjects with any grade cytokine release syndrome (CRS) had 2.31-fold, 2.41-fold, and 1.19-fold higher median C_{max} (p=0.0002), AUC_{0-28d} (p<0.0001), and expansion rate (p<0.0001), respectively, than subjects without any grade CRS. (Table 16).

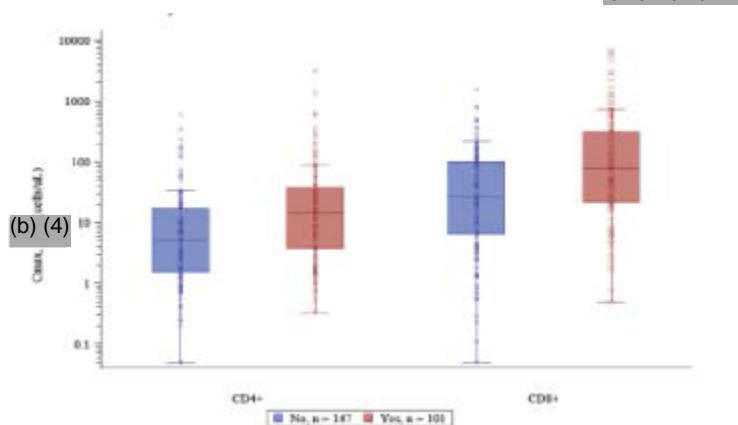
Table 16. Summary of JCAR017 Expansion and Cytokine Release Syndrome

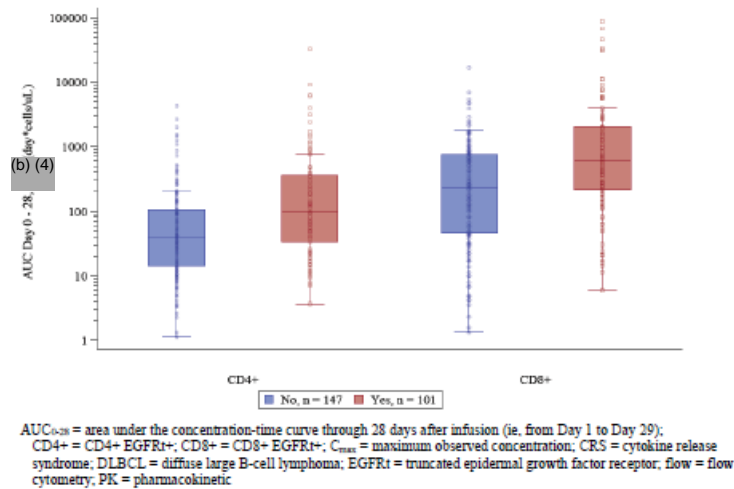
PK Parameters (Median (range))	CRS	No CRS
N	95	143
C _{max} (copies/μg DNA)	43756.1 (1268.4, 539903.0)	18937.0 (29.3, 467249.0)
T _{max} (days)	11.0 (6.0, 41.0)	13.0 (6.0, 112.0)
AUC _{0-28d} (day* copies/μg DNA)	380670.8 (12119.0, 8539093.0)	157771.1 (344.0, 5144642.0)
Expansion Rate (copies/μg DNA/day)	3499.9 (46.3, 37634.7)	1600.6 (2.3, 47470.4)

Due to the small sample size for subjects with severe CRS (n=5), exposure-response analysis was not conducted for subjects with severe CRS and subjects with Grade 0-2 CRS.

Exploratory analysis was performed using (b) (4) measurements. Similar results were observed for CD4+ EGFRt+ T cells and CD8+ EGFRt+ T cells (Figure 6, Table 17).

Figure 6. Box Plot of C_{max} and AUC_{0-28d} for CD4+ EGFRt+ T cells and CD8+ EGFRt+ T cells by CRS Status (DLBCL Cohort, Single-dose Schedule, (b) (4) Analysis)





Source: Applicant. Figure 3 in section 1.11.3. Response to information request No. 37.

Table 17. Summary of Correlative Analysis Between JCAR017 PK and Safety Responses (DLBCL Cohort, Single-dose Schedule, (b) (4) Analysis)

	Transgene (JCAR017-017001-ClinPharm Report)		CD8+ EGFRt+		CD4+ EGFRt+		CD4+ EGFRt+/CD8+ EGFRt+	
	C _{max}	AUC ₀₋₂₈	C _{max}	AUC ₀₋₂₈	C _{max}	AUC ₀₋₂₈	C _{max} ratio	AUC ₀₋₂₈ ratio
CRS vs. no CRS, median fold-change ^a	2.31-fold higher; p = 0.0002	2.41-fold higher; p < 0.0001	3.07-fold higher; p < 0.0001	2.64-fold higher; p < 0.0001	2.92-fold higher; p < 0.0001	2.54-fold higher; p < 0.0001	0.19 vs. 0.17; p = 0.4590	0.18 vs. 0.18; p = 0.3686
iiNT vs. no iiNT, median fold-change ^a	3.46-fold higher; p < 0.0001	3.88-fold higher; p < 0.0001	4.23-fold higher; p < 0.0001	3.44-fold higher; p < 0.0001	4.36-fold higher; p < 0.0001	4.82-fold higher; p < 0.0001	0.25 vs. 0.16; p = 0.2851	0.25 vs. 0.17; p = 0.2647
Grade ≥3 iiNT vs. Grade 0-2 iiNT, median fold-change ^a	5.06-fold higher; p = 0.0001	5.99-fold higher; p < 0.0001	5.15-fold higher; p < 0.0001	3.93-fold higher; p < 0.0001	13.28-fold higher; p < 0.0001	19.24-fold higher; p < 0.0001	0.25 vs. 0.17; p = 0.5104	0.29 vs. 0.18; p = 0.3959

AUC₀₋₂₈ = area under the concentration-time curve through 28 days after infusion (ie, from Day 1 to Day 29); CI = confidence interval; C_{max} = maximum observed concentration; CRS = cytokine release syndrome; DOR = duration of response; EGFRt = truncated epidermal growth factor receptor; iiNT = investigator-identified neurologic toxicity; IRC = Independent Review Committee; PFS = progression-free survival; PK = pharmacokinetics

^aMedian value of each subgroup is displayed for the ratio of C_{max} or AUC₀₋₂₈ (CD4+ EGFRt+/CD8+ EGFRt+).

Note: All p-values are reported as 2-sided without multiplicity adjustment. The number of subjects with Grade ≥ 3 CRS in the analyses was too small (N = 5) to assess the relationship with PK.

Source: Applicant. Table 2 in section 1.11.3. Response to information request No. 37.

Exposure and Neurologic Toxicities

Subjects with any grade neurologic toxicities (NT) had 3.46-fold, 3.88-fold, and 1.87-fold higher median C_{max} (p=0.0002), AUC_{0-28d} (p<0.0001), and expansion rate (p<0.0001), respectively, than subjects without any grade NT. (Table 18).

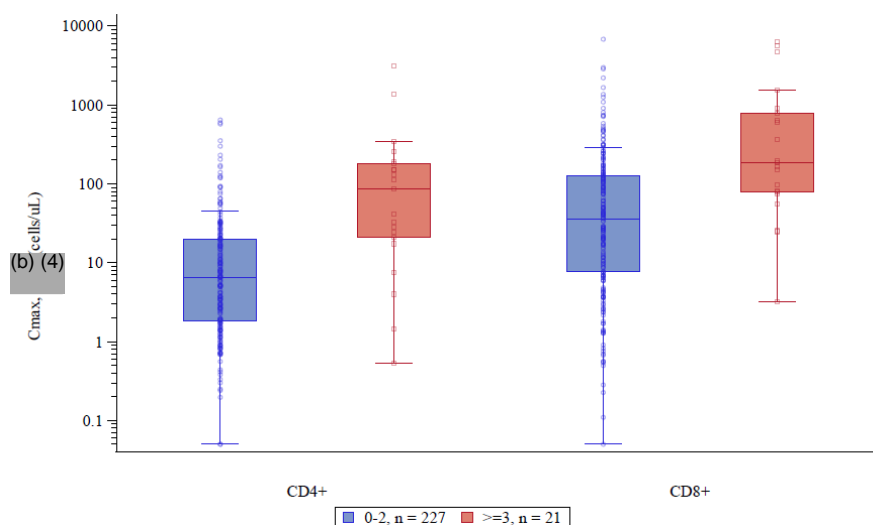
Table 18. Summary of JCAR017 Expansion and Neurologic Toxicities (b) (4) Assay)

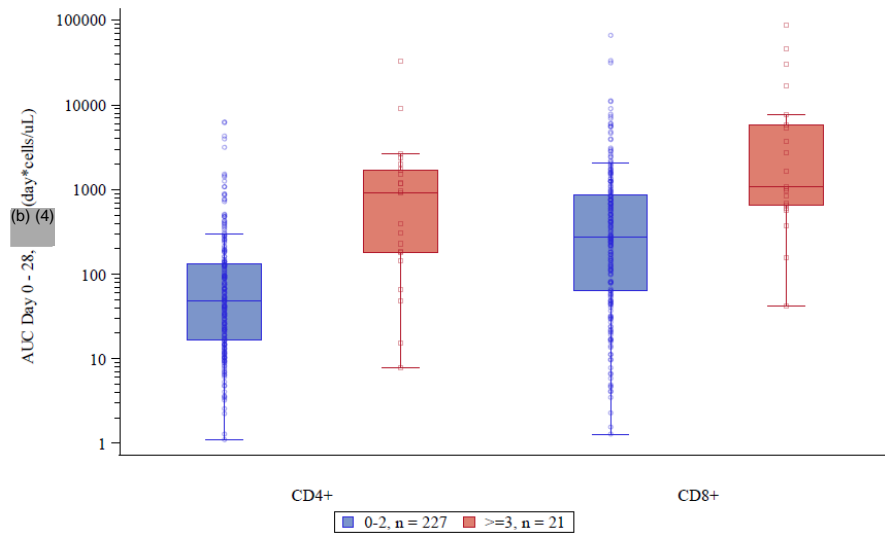
PK Parameters (Median (range))	NT (Any Grade)	No NT
N	70	168
C _{max} (copies/μg DNA)	66606.6 (1897.5, 539903.0)	6841.9 (29.3, 467249.0)
T _{max} (days)	12.5 (6.0, 41.0)	12.0 (6.0, 112.0)
AUC _{0-28d} (day* copies/μg DNA)	622692.3 (15505.0, 8539093.0)	160665.9 (344.0, 4280362.0)
Expansion Rate (copies/μg DNA/day)	4798.3 (46.3, 37408.5)	1673.7 (552.9, 4269.4)

Based on PK measurements using (b) (4) assay, subjects with severe (Grade ≥ 3) NT had a 5.05-fold, 5.99-fold, and 3.85-fold higher median C_{max} (p=0.2322), AUC_{0-28d} (p=0.0954), and expansion rate (p=0.0004), respectively, than subjects with Grade 0-2 NT.

Exploratory analysis was performed using (b) (4) measurements. Similar to the observations of (b) (4) PK measurements, subjects with any grade neurologic toxicities had higher exposure of CD3+EGFRt+, CD3+EGFRt+, and CD3+EGFRt+ T cells. As noted in Table 17, the expansion (C_{max} and AUC_{0-28d}) of CD4+ EGFRt+ T cells in subjects with severe (Grade ≥ 3) NT was substantially higher than subjects with Grade 0-2 NT (Figure 7 & Figure 8).

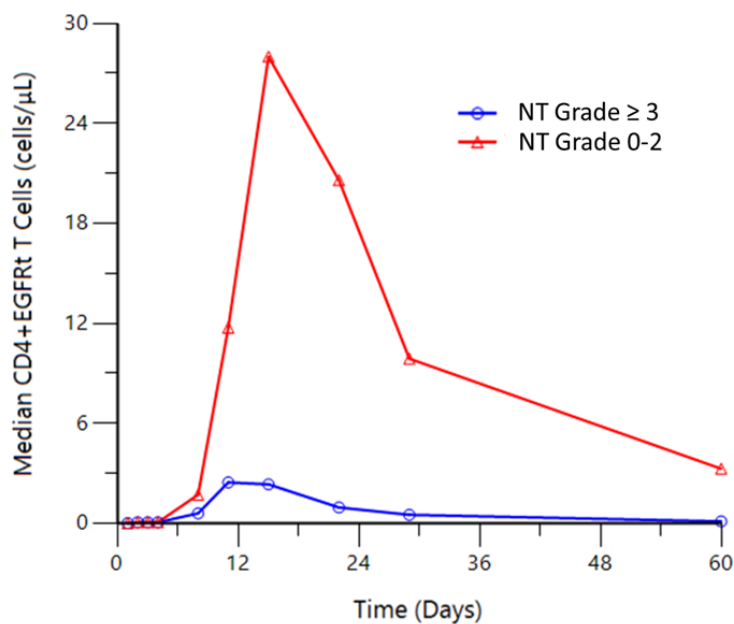
Figure 7. Box Plot of C_{max} and AUC_{0-28d} for CD4+ EGFRt+ T cells and CD8+ EGFRt+ T cells by Neurologic Toxicities Status (DLBCL Cohort, Single-dose Schedule, (b) (4) Assay)





Source: Applicant. Figures 1.5 & 1.10 in section 1.11.3. Response to information request No. 37 Tables and Figures.

Figure 8. Comparison of CD4+EGFRt+ T Cells Cellular Kinetic/Pharmacokinetic Profiles between Subjects with Severe (Grade ≥ 3) Neurologic Toxicities and Subjects with Grade 0-2 Neurologic Toxicities (DLBCL Cohort, Single-Dose)



Logistic regression indicated that CD4+EGFRt+ T cells expansion (Cmax, AUC_{0-28d}, and expansion rate) was positively associated with incidence of severe neurologic toxicities (Grade \geq 3) (Table 19).

Table 19. Logistic Regression Analysis Between CD4+EGFRt+ T Cells Expansion and Severe Neurologic Toxicities (DLBCL Cohort, Single-Dose Schedule, (b) (4) Assay)

Log Cmax			
	Odds Ratio	p value	95% CI
Intercept	0.0119	3.80E-13	0.0031 – 0.0350
LogCmax	4.7514	7.75E-06	2.4937 – 9.9196
Log AUC _{0-28d}			
	Odds Ratio	p value	95% CI
Intercept	0.0024	3.95E-11	0.0003 – 0.0124
LogAUC _{0-28d}	5.0685	2.76E-06	2.6727 – 10.5378
Log Expansion Rate			
	Odds Ratio	p value	95% CI
Intercept	0.0660212	< 2E-16	0.0335 – 0.1150
LogExpansionRate	4.9628	1.65E-05	2.5014 – 10.9227

6.1.2.3 Pharmacodynamics

For pharmacodynamics assessment in Study 17001, the applicant evaluated the following PD endpoints: B-cell aplasia, serum immunoglobulins, serum soluble biomarkers, C-reactive protein (CRP) and ferritin.

6.1.2.3.1 B-Cell Aplasia

Treatment of anti-CD19 CAR T cells may induce B-cell aplasia. B cell aplasia was defined as CD19+ B cells comprising less than 3% of peripheral blood lymphocytes. The incidence of B-cell aplasia was assessed a qualified (b) (4) assay. As shown in Table 20, the percentage of B-cell aplasia increased from baseline level of 92% to 98% on Day 29 and returned to baseline level on Day 90. No clear dose-response relationship was observed between B-cell aplasia and JCAR017 across all dose levels.

Table 20. Incidence of B-cell Aplasia by JCAR017 Dose Level (DLBCL Cohort)

Visit	B-cell aplasia, x/n (%)				
	DL1S N = 45	DL2S N = 176	DL3S N = 41	DL1S + DL2S + DL3S N = 262	DL1D ^a N = 6
Baseline	41/45 (91)	162/176 (92)	38/41 (93)	241/262 (92)	5/6 (83)
Day 29	41/41 (100)	160/163 (98)	39/40 (98)	240/244 (98)	6/6 (100)
Day 60	34/34 (100)	127/132 (96)	27/27 (100)	188/193 (97)	4/4 (100)
Day 90	26/26 (100)	101/111 (91)	16/18 (89)	143/155 (92)	3/3 (100)
Day 180	17/18 (94)	66/77 (86)	6/6 (100)	89/101 (88)	3/3 (100)
Day 270	15/17 (88)	41/53 (77)	0/0	56/70 (80)	3/3 (100)
Day 365	11/14 (79)	25/35 (71)	0/0	36/49 (73)	3/3 (100)

DLBCL = diffuse large B-cell lymphoma; DL1D = Dose Level 1, 2-dose regimen; DL1S = Dose Level 1, single-dose regimen; DL2S = Dose Level 2, single-dose regimen; DL3S = Dose Level 3, single-dose regimen; N = number of subjects in the population; n = number of subjects for evaluation; x = number of subjects with B-cell aplasia

Note: JCAR017-treated Analysis Set includes all subjects who have received at least 1 dose of JCAR017. Values after initiation of another anticancer treatment are excluded from the summaries. Baseline was the last value prior to JCAR017 infusion. B-cell aplasia is defined as CD19+ < 3% lymphocytes.

^a B-cell aplasia after Day 29 for DL1D were based on data after the second infusion.

Source: Applicant. Table 10 of section 5.3.4.2. Study 17001 Clinical Pharmacology Report, page 49.

6.1.2.3.2 Serum Immunoglobulins

The applicant evaluated serum immunoglobulin levels in the DLBCL cohort. No clear difference in hypogammaglobulinemia (ie, IgG < 500 mg/dL) was observed amongst different dose levels. At baseline, about 48% subjects had hypogammaglobulinemia. The % of subjects with hypogammaglobulinemia did not change substantially after administration of JCAR017. The % of subjects with hypogammaglobulinemia was 58%, 60%, 66%, and 61% on Day 29, 60, 180, and 365, respectively.

6.1.2.3.3 Soluble Biomarkers

The applicant measured a panel of 41 soluble biomarkers, including IL-6 and IL-10. The levels of most soluble biomarkers increased to peak within the first 14 days after JCAR017 infusion, and then returned to baseline levels within 28 days post infusion.

6.1.2.3.4 C-reactive Protein and Ferritin

Levels of serum CRP were elevated on Day 1 prior to infusion and decreased to 80% within the first 28 days after infusion. Serum ferritin levels were elevated at baseline and remained relatively unchanged during the first 28 days after JCAR017 administration.

6.1.2.3.5 Pharmacodynamic – Response Relationship

Correlative analysis was conducted to assess the relationship between pharmacodynamic biomarkers and safety and efficacy of JCAR017 treatment. No associations were identified between PD biomarkers and efficacy.

Pharmacodynamic – Safety Relationship

The relationship between PD biomarkers and cytokine release syndrome (CRS) and neurological toxicities were evaluated. The relationship between PD biomarkers and Grade ≥ 3 CRS was not assessed due to small sample size (n=6); however, the relationship with any grade CRS was evaluated.

Pharmacodynamic Biomarkers and Cytokine Release Syndrome (CRS)

Baseline levels

Higher baseline levels of the following biomarkers were observed in subjects with CRS than subjects with no CRS (p<0.05): intercellular adhesion molecule 1 (ICAM1), IL-6, macrophage inflammatory protein 1 α (MIP1 α), serum amyloid A1 (SAA1), and TNF α .

As shown in Table 21, compared to subjects who did not have CRS, subjects with any grade CRS had a 3.23-fold and 1.82-fold higher median baseline CRP and ferritin levels, respectively.

Table 21. Median Baseline CRP and Ferritin Levels by CRS Status (DLBCL Cohort, Single-dose schedule)

Variable (units)	Statistic	Subjects with CRS	Subjects without CRS	Multiplicity-adjusted p-value ^a
CRP (mg/L)	n	110	151	
	Median	53.9	16.7	0.0008
	Q1, Q3	13.3, 116.0	6.7, 60.0	
Ferritin (μ g/L)	n	110	151	
	Median	745.5	410.0	0.0281
	Q1, Q3	270.0, 1522.0	170.0, 999.1	

CRP = C-reactive protein; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; n = number of subjects tested; Q1, Q3= first and third quartiles

^a p-value based on the Wilcoxon test and adjusted for multiplicity using the Holm step-down Bonferroni method.

Source: Applicant. Table 19 in section 5.3.4.2. Study 17001 Clinical Pharmacology Report, page 75.

Peak Levels after JCAR017 Administration

After JCAR017 infusion, transient elevations of soluble biomarkers such as cytokines, chemokines were observed. Peak elevation of soluble biomarkers was observed within the first 14 days post JCAR017 infusion and returned to baseline levels within 28 days.

Peak levels of 25 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IFN γ -induced protein 10 (IP-10), MIP1 α , transforming growth factor beta 3 (TGF β 3), and TNF α were positively associated with CRS.

Subjects with CRS (n=110) had a 4.0-fold and 2.48-fold higher median peak CRP and ferritin levels, respectively, compared to subjects who did not have CRS (n=152).

Pharmacodynamic Biomarkers and Neurologic Toxicities (NT)

Baseline Levels

Higher baseline levels of the following biomarkers were observed in subjects with neurologic toxicities (NT) than subjects with no NT (p<0.05): ICAM1, IL-6, IL-10, MIP1 α , SAA1, TNF α , and vascular cell adhesion molecule 1 (VCAM1).

Higher baseline levels of following biomarkers were observed in subjects with severe (Grade \geq 3) NT than subjects with Grade <3 or no NT (p<0.05): IL-6, IL-8, IL-10, and MIP1 α .

Subjects with any grade NT had a 3.04-fold and 1.83-fold higher median baseline CRP and ferritin levels, respectively, compared to subjects who did not have NT (CRP: 59.6 vs. 19.6 mg/L, p=0.0071; ferritin: 782.0 vs. 427.3 μ g/L, p=0.0614).

As shown in Table 22, compared to subjects with Grade 0-2 NT, subjects with Grade \geq 3 NT had a 2.85-fold and 3.28-fold higher median baseline CRP and ferritin levels, respectively.

Table 22. Median Baseline CRP and Ferritin Levels by Grade \geq 3 NT Status (DLBCL Cohort, Single-dose schedule)

Variable	Statistic	Subjects with Grade \geq 3 iiNT	Subjects with Grade 0-2 iiNT	Multiplicity-adjusted p-value ^a
CRP (mg/L)				
	n	26	235	
	Median	68.4	24.0	0.0575
	Q1, Q3	31.0, 137.4	6.8, 76.9	
Ferritin (μ g/L)				
	n	26	235	
	Median	1521.5	464.0	0.0133
	Q1, Q3	620.0, 2749.0	207.0, 1090.2	

CRP = C-reactive protein; DLBCL = diffuse large B-cell lymphoma; iiNT = investigator-identified neurologic toxicity; n = number of subjects tested; Q1, Q3 = first and third quartile.

Source: Applicant. Table 21 in section 5.3.4.2. Study 17001 Clinical Pharmacology Report, page 76.

Peak Levels after JCAR017 Administration

Higher peak levels of 22 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IL-10, IP-10, MIP1 α , and TNF α were associated with any grade of NT.

Higher peak levels of 13 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IL-10, IP-10, MIP1 α , and TNF α were associated with severe NT (grade ≥ 3).

Subjects with NT (any grade, n=79) had a 3.46-fold and 2.55-fold higher median peak CRP and ferritin levels, respectively, compared to subjects who did not have NT (n=183).

Subjects with severe NT (Grade ≥ 3) (n=26) had a 3.05-fold and 5.16-fold higher median peak CRP and ferritin levels, respectively, compared to subjects with Grade 0-2 NT (n=236).

6.1.2.4 Immunogenicity

The prevalence and incidence of anti-therapeutic antibodies (ATA) were evaluated for JCAR017. In the DLBCL Cohort, 28 of 261 subjects (10.7%) had pre-existing ATA at baseline. The incidence of ATA was 10.5% (27 of 257 subjects): 23 subjects had treatment-induced ATA and 4 subjects had treatment-boosted ATA. There were no clear differences in the prevalence and incidence of ATA among different dose levels.

As shown in Table 23, JCAR017 expansion was compared between subjects with and without pre-existing ATA and between subjects with and without ATA incidence. Due to the small number of subjects who had pre-existing ATA, treatment-induced or treatment-boosted ATA, the impact of immunogenicity on JCAR017 expansion was not conclusive.

Table 23. JCAR017 Expansion (C_{max} and AUC_{0-28d}) vs. Anti-therapeutic Antibodies

	Anti-Therapeutic Antibody Prevalence ^a		Anti-Therapeutic Antibody Incidence ^b	
	Yes N=26	No N=228	Yes N=27	No N=223
Transgene				
C _{max} , qPCR (copies/ug)				
n	22	210	27	205
Mean (StD)	97879.0 (116913.40)	66461.9 (102181.70)	53625.5 (66027.24)	71524.2 (107737.34)
Median	50908.6	23654.6	31583.4	23928.2
Q1, Q3	18530.7, 164897.8	8082.9, 77218.8	7643.0, 89868.3	8185.7, 78748.2
Min, Max	3523, 415118	29, 539903	2367, 301078	29, 539903
CV%	119.4	153.7	123.1	150.6
Geometric Mean (CV%)	44802.1 (251.8)	23423.8 (357.5)	26109.6 (220.9)	24755.6 (374.1)

	Anti-Therapeutic Antibody Prevalence ^a		Anti-Therapeutic Antibody Incidence ^b	
	Yes N=26	No N=228	Yes N=27	No N=223
Transgene				
AUC Day 0 - 28, qPCR (day*copies/ug)				
n	22	210	27	205
Mean (StD)	1079424.1 (1700505.41)	655822.9 (1200479.78)	481206.4 (604920.18)	724280.8 (1318377.47)
Median	430482.6	203703.1	197363.8	215081.2
Q1, Q3	122845.3, 1303291.7	74964.1, 657096.0	81583.7, 535721.1	77281.7, 731228.7
Min, Max	44657, 6646582	344, 8539093	20152, 2326814	344, 8539093
CV%	157.5	183.0	125.7	182.0
Geometric Mean (CV%)	424966.9 (265.3)	210437.5 (362.3)	219590.2 (233.4)	225654.8 (380.2)

Source: Applicant submission. Study 017001 Report Appendix-a, Table 14.3.4.10.4.

6.1.2.5 Replication-competent Lentivirus (RCL)

JCAR017 comprises lentiviral vector transduced T cells, the presence of replication-competent lentivirus (RCR) in the blood of treated subjects were monitored. No subjects were found to be RCL positive.

6.1.3 Conclusions

General Cellular Kinetics/Pharmacokinetics

- JCAR017 cellular kinetics comprise lag, expansion, contraction and persistence phases in treated subjects. Following infusion, JCAR017 exhibited an initial expansion followed by a bi-exponential decline. The median time to reach peak levels in peripheral blood was 12 days post-dose. Persistence of JCAR017 transgene was observed up to 2 years.
- Compared to CD4+ EGFRt+ subset T cells, CD8+ EGFRt+ subset T cells had higher expansion after infusion.
- Some subjects in Study 17001 received additional doses of JCAR017 per the following regimens: two-dose schedule, retreatment cycles, and additional cycles.
 - In the two-dose schedule, the second dose infusion (14 days after first dose) did not increase JCR017 expansion. The cellular kinetics/pharmacokinetics for the two-dose schedule were similar to the single-dose schedule.
 - Subjects with retreatment cycles or additional cycles treatment had substantially lower JCAR017 expansion, compared to subjects who received single-dose JCAR017 treatment.

Critical Factors Impacting JCAR017 Cellular Kinetics/Pharmacokinetics

- With increased age, JCAR017 expansion decreased. Subjects < 65 years old had a 3.06-fold and 2.30-fold higher median C_{max} and AUC_{0-28d}, respectively, compared to subjects ≥ 65 years old.
- Subjects with higher tumor burden (sum of product of perpendicular diameters (SPD) prior to LDC of ≥ 50 cm²) had a 2.86-fold and 2.45-fold higher median AUC_{0-28d} and C_{max}, respectively, compared to subjects with an SPD prior to LDC of < 50 cm².
- The following product characteristics showed positive correlative relationships with JCAR017 expansion: IL-2 and TNFα secreted by CD4+CAR+ T cells, frequency of CD3+CD8+ CAR T cells, frequency of CCR7+CD8+CAR+ T cells, and CD27+CD8+CAR+ T cells. Higher frequency of CD28+ CD4+CAR+ T cells and apoptosis of CD8+CAR+ T cells were associated with higher T_{max} values.

Drug-Drug Interactions

- Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with JCAR017. JCAR017 continued expansion in subjects who received tocilizumab and corticosteroids after infusion of JCAR017.

Exposure-Response Relationship

- No clear dose-response of JCAR017 in PK (b) (4) data), PD and immunogenicity was observed in the DLBCL cohort.
- Responders (CR and PR) had a 2.48-fold, 1.91-fold and 2.13-fold higher median C_{max}, AUC_{0-28d}, and expansion rate, respectively, compared to non-responders (SD and PD) (b) (4) data). (b) (4) data showed similar trend with CD3+EGFRt+, CD4+EGFRt+, and CD8+EGFRt+ T cells. Higher expansion of CD3+EGFRt+, CD4+EGFRt+ T cells were positively associated with best overall response (BOR).
- Higher JCAR017 exposure was associated with higher incidence of any grade cytokine release syndrome (CRS) and neurologic toxicities (NT).
- (b) (4) assay data indicated that subjects with Grade ≥ 3 neurologic toxicities (NT) had substantially higher (more than 10-fold higher) median C_{max} and AUC_{0-28d}, and expansion rate for CD4+EGFRt+, respectively, compared with subjects with Grade 0-2 NT.

Pharmacodynamics

- B-cell aplasia (defined as CD19+ B cells comprising less than 3% of peripheral blood lymphocytes) is observed in majority of JCAR017 treated subjects for up to 1 year.

- Transient elevations of soluble biomarkers such as cytokines, chemokines were observed after infusion of JCAR017. Peak elevation of soluble biomarkers was observed within the first 14 days post JCAR017 infusion and returned to baseline levels within 28 days.
- Higher baseline levels of the following biomarkers were observed in subjects with any grade of CRS compared to subjects with no CRS: c-reactive protein (CRP), ferritin, intercellular adhesion molecule 1 (ICAM1), IL-6, macrophage inflammatory protein 1 α (MIP1 α), serum amyloid A1 (SAA1), and TNF α .
- Higher baseline levels of the following biomarkers were observed in subjects with any grade of neurologic toxicities (NT) compared to subjects with no NT: c-reactive protein (CRP), ferritin, ICAM1, IL-6, IL-10, MIP1 α , SAA1, TNF α , and vascular cell adhesion molecule 1 (VACM1).
- Peak levels of 25 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IFN γ -induced protein 10 (IP-10), MIP1 α , transforming growth factor beta 3 (TGF β 3), and TNF α were associated with CRS.
- Peak levels of 22 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IL-10, IP-10, MIP1 α , and TNF α were associated with NT.

Immunogenicity

- Prevalence and incidence of anti-therapeutic antibody (ATA) was approximately 10%. The relationship b/w ATA status and JCAR017 PK was not conclusive due to small number of subjects who had pre-existing ATA, treatment-induced or treatment-boosted ATA.

Replication-competent Lentivirus (RCL) Testing

- No RCL has been detected in the blood in any treated subjects.