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 (DCEPT)

Submission Number: BLA 125714.90

Product Name: Lisocabtagene maraleucel (BREYANZI)

Proposed Indication: treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- relapsed or refractory disease after two or more lines of systemic therapy.

Applicant: Juno Therapeutics, Inc. a Bristol-Myers Squibb

Date Submitted: December 23, 2021

RPM: Niloofar Kennedy

Reviewer: Million Tegenge, PhD

Clinical Pharmacology Reviewer, General Medicine Branch 2, DCEPT, OTAT

Through: Tejashri Purohit-Sheth, MD

Director, DCEPT, OTAT

Table of Contents

1. Executive Summary

BREYANZI (lisocabtagene maraleucel) is a CD19-directed, genetically modified autologous T cell immunotherapy administered as a defined composition of CAR-positive viable T cells (consisting of CD8 and CD4 components). Currently, BREYANZI has FDA approved indication for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. In this BLA efficacy supplement, the applicant is seeking approval for the treatment of adult patients with large B-cell lymphoma after at least one prior therapies (LBCL).

The clinical pharmacology data were collected from two clinical studies (#BCM-003 and #017006). For clinical pharmacology comparative evaluation, the previously reviewed and approved Study (#017001) is considered as reference study. In Study #BCM-003, the PK analysis indicate comparability of Cmax, Tmax and AUC between subjects who crossover from standard of care (SOC) and BREYANZI arm. The clinical pharmacology comparative evaluation between the two relevant studies (#017006 vs #017001) showed no major difference in Tmax, Cmax, AUC and persistence.

The exposure-efficacy analysis did not reveal statistically significant difference between responder and non-responder subjects (#BCM-003 and #017006). In Study #BCM-003, a potential association was observed between higher transgene Cmax or AUC(0-28d) and higher incidence of any grade CRS or any grade investigator-identified neurologic toxicity (iiNT). The relationship between PK parameters and grade ≥ 3 CRS or iiNT was not assessed because of the limited number of subjects with grade ≥ 3 CRS (n = 1) or iiNT (n=4). As previously observed, subjects treated with tocilizumab or corticosteroids have a higher Cmax and AUC (0-28) as compared to subjects who did not receive tocilizumab or corticosteroids.

In Study #BCM-003, the prevalence and incidence of anti-therapeutic antibodies (ATA) was 2.2% (3 of 135 subjects) treated with BREYANZI. In Study#017006, at baseline none

of the subjects has AT, and after treatment with BREYANZI one patient (2%) developed ATA (1 of 49 subjects). Due to small sample size, it is not possible to fully evaluate the impact of ATA on efficacy, safety, or PK.

Overall, experience from the previous and current dose-response, PK and exposure-response analysis support the applicant's proposed dose of 90-110 million CAR-positive viable T cells of BREYANZI for treatment of adult subjects with large B-cell lymphoma after at least 1 prior therapies (LBCL).

2. Recommendations

This BLA efficacy supplement is acceptable for approval from the clinical pharmacology perspective.

3. Background

BREYANZI (lisocabtagene maraleucel) is a CD19-directed genetically modified autologous T cell immunotherapy administered as a defined composition of CAR-positive viable T cells (consisting of CD8 and CD4 components). The CAR is comprised of the 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 activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion T cell and persistence. 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.

Currently, BREYANZI is FDA approved indication for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

In this BLA efficacy supplement, the applicant is seeking approval for the treatment of adult patients with large B-cell lymphoma after at least one prior therapies (LBCL). The current submission is supported by two clinical studies:

- Study JCAR017-BCM-003, entitled: “A Global Randomized Multicenter Phase3 Trial to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Patients with High-Risk, Transplant-Eligible Relapsed or Refractory Aggressive B-Cell Nonhodgkin Lymphomas”.
- Study 017006, entitled: “A Phase 2 study of Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-cell NHL (017006)”.

4. Summary of Clinical Pharmacology Findings

The data supporting clinical pharmacology assessments were obtained from Study JCAR017-BCM-003 (hereafter referred to as Study #BCM-003) and Study #017006. For clinical pharmacology comparative evaluation, the previously reviewed and approved Study (#017001) is considered as reference study. The major clinical pharmacology findings are summarized in the following sections.

Dose Selection and Justification

- The selected target dose for study #BCM-003 and #017006 was 100 × 10^6 CAR+ T cells that was based on previous clinical experience (study #017001).
- In the previous dose finding study (#017001), there was no evident dose-exposure and dose-response relationship across the three dose levels (50, 100,150 million cells) and FDA approved dosing of BREYANZI was 50 to 110 million CAR-positive viable T cells.
- Overall, experience from the previous and current clinical pharmacology studies support the applicant proposed target dose of 100 million CAR-positive viable T cells of BREYANZI for treatment of adult subjects with large B-cell lymphoma after at least one prior therapies (LBCL).

Pharmacokinetic (PK) Assessments

- The PK of BREYANZI is characterized by an initial expansion phase and a bi-exponential decline following intravenous administration.
- In Study #BCM-003, the PK analysis indicate comparability of Cmax, Tmax and AUC between subjects who crossover from standard of care (SOC) and BREYANZI arm. Thus, from this PK comparability assessment we may infer no impact of prior therapies (i.e., HDCT and HSCT as part of SOC) on CAR-T cells exposure parameters.

- In Study #BCM-003, subjects treated with tocilizumab (n = 18) had a 2.3-fold and 4.0-fold higher median transgene Cmax and AUC (0-28), respectively, compared to subjects who did not receive tocilizumab (n = 65).
- Subjects who received corticosteroids (n = 12) had a 3.5-fold and 3.9-fold higher median transgene Cmax and AUC (0-28), respectively, compared with subjects who did not receive corticosteroids (n = 71).
- The difference in study design, sample size and bioassay methods preclude direct comparison of clinical pharmacology results from #BCM-003 with the other two studies. The clinical pharmacology comparative evaluation between the two relevant studies (#017006 vs #017001) showed no major difference in Tmax, Cmax, AUC and persistence as shown in the Table below:

	#017001(DLBCL cohort) N=238[a]	**#017006 N=55[a]**
Cmax (copies/µg)	23964 (8159, 78748)	23000 (12012, 52628)
Tmax(day)	12 (10, 15)	10 (8, 14)
AUC (0-28) (day*copies/µg)	214283 (77282, 689752)	222758 (2376, 2093636)
Persistence (% subjects with detectable transgene)	Day 29: 232/236 (98%) Day 180: 58/88 (66%) Day 365: 22/37 (59%) Day 730: 3/8 (38%)	Day 29: 47/50 (94%) Day 180: 20/31 (65%) Day 365: 9/15 (60%) Day 730: 0/2 (0%)

Pharmacodynamic (PD) Assessments

- B-cell aplasia, defined as < 3% of CD19+ B cells in peripheral blood lymphocyte, is on target, off tumor pharmacodynamic effect of BREYANZI.
- In Study #BCM-003 & #017006, B-cell aplasia was observed in 95-100% of subjects at 2-3 months following BREYANZI treatment.

- In Study #BCM-003, the peak levels for IL-6 and IFN-gamma were observed within 10 days after BREYANZI infusion and returned to baseline levels by 35 days.
- The median baseline level of C-reactive protein (CRP) was 5.31 mg/L and increased to 9.3 mg/L at day 36 following BREYANZI infusion. From days 53 to 120, the CRP level varied between 1.9 to 3.0 mg/L.

Immunogenicity Risk Assessments

- Incidence of anti-therapeutic antibodies (ATA) is defined as the percentage of subjects with treatment-induced or treatment-boosted antibodies that bind to BREYANZI.
- In Study #BCM-003, the prevalence and incidence of ATA was 2.2% (3 of 135 subjects) treated with BREYANZI.
- In Study#017006, at baseline none of the subjects had AT, and after treatment with BREYANZI one patient (2%) developed ATA (1 of 49 subjects).
- Due to small sample size, it was not possible to fully evaluate the impact of ATA on efficacy, safety, or PK.

Exposure-Efficacy Assessments

- In the reference study (# 017001), higher transgene Cmax and AUC (0-28) were associated with a higher overall response and complete response rate.
- In Study #BCM-003, the exposure-efficacy analysis did not reveal statistically significant difference between responder and non-responder subjects. The median Cmax in responders (N=76) and non-responders (N=7) was 33,285 copies/µg and 95,618 copies/µg, respectively. This finding was somewhat unexpected based on the experience from the previous study (#017001) that showed responders (N=135) had a 2.3-fold higher median Cmax than non-responders (N=37) (35,335 vs. 15,527 copies/µg). This discrepancy could be due to the difference in patient population, sample size, dose range and PK variability.

- In Study #017006, a potential association was observed between earlier transgene Tmax and CR, and higher Cmax and longer PFS. No other apparent relationships were observed between transgene PK parameters and efficacy endpoints.

Exposure-Safety Assessments

- In the reference study (# 017001), higher transgene Cmax and AUC (0-28d) were associated with a higher incidence of any grade CRS, any grade investigator-identified neurologic toxicity (iiNT), and Grade ≥ 3 iiNT.
- In Study #BCM-003, a potential association was observed between higher transgene Cmax or AUC(0-28d) and higher incidence of any grade CRS. A similar potential association was observed between higher transgene or AUC(0-28d) and higher incidence of any grade iiNT. The relationship between PK parameters and grade ≥ 3 CRS or iiNT was not assessed because of the limited number of subjects with grade ≥ 3 CRS (n = 1) or iiNT (n=4).
- In Study #017006, a potential association was observed between earlier transgene Tmax and higher incidence of any grade CRS and between higher transgene Cmax and higher incidence of any grade iiNT. The frequency of Grade ≥ 3 CRS and iiNT was too low to assess any potential relationship with these events.

5. Clinical Pharmacology Labeling Comments

The following are clinical pharmacology labeling comments communicated to the Applicant:

Section 12.3: Pharmacokinetics

- Update Tmax and CAR T cell persistence
- Requested to clarify exposure change with use of tocilizumab and corticosteroids and reflect association of exposure parameters with CRS and neurotoxicity.
- Requested to remove PK results from study #BCM-003 and Study #017006 due to issues with PK interpretability (e.g., change in bioassay, limited nonresponding subjects, high variability).

6. Appendix

6.1 Study JCAR017-BCM-003: A Global Randomized Multicenter Phase 3 Trial to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Patients with High-Risk, Transplant-Eligible Relapsed or Refractory Aggressive B-Cell Nonhodgkin Lymphomas

The primary objective of the study was to compare the efficacy in subjects treated with BREYANZI versus subjects treated according to standard of care (SOC). The clinical pharmacology objectives include evaluation of:

- pharmacokinetic (PK) profile of BREYANZI
- pharmacodynamic markers of BREYANZI, including B-cell aplasia and soluble biomarkers such as chemokines and cytokines
- immune responses directed against BREYANZI

Overall Study Design and Plan:

The following four periods are included in the study design:

- **Screening** (Study Days -28 to -1): consisted of screening assessments to determine eligibility for randomization and unstimulated leukapheresis for all eligible subjects prior to randomization (irrespective of treatment arm)
- **Treatment Period** (Study Days 1 [+ 3 days] to 126 [± 7 days]): consisted of randomization to either Arm A (SOC followed by high-dose chemotherapy (HDCT) and hematopoietic stem cell transplant (HSCT)) or Arm B (bridging therapy [if needed], LDC followed by BREYANZI infusion Day 29 ± 7 days (2 to 7 days after completion of LDC]). The first response evaluations were performed at Week 9 (after 3 cycles of SOC for Arm A and 5 weeks after BREYANZI infusion for Arm B) and Week 18 (8 weeks after the start of HDCT for Arm A and 14 weeks after lisocel infusion for Arm B).

- **Post-treatment Period**: consisted of further efficacy and safety follow-up visits at Month 6 (± 10 days), 9, 12, 18, 24, and 36 (± 14 days) (end of study [EOS]) or early termination (ET).
- **Survival Follow-up:** After the EOS visit, Survival Follow-up visits were scheduled every 3 months (± 30 days) until last subject last visit.

Pharmacokinetic assessment: The transgene levels were determined in the collected blood samples using the droplet digital PCR (ddPCR) and optionally by flow cytometry techniques. Transgene levels were reported in copies/µg DNA. For BREYANZI treated subjects, peripheral blood samples for cellular kinetics analysis were collected as follows:

- Pre-infusion
- Post-infusion of BREYANZI at days 3, 4, 8, 11,15, 22, 29
- Post-infusion of BREYANZI at months 2, 3, 6, 9 and 12

For PK analysis data sets, noncompartmental PK parameters, including Cmax, Tmax, AUC (0-28), and expansion rate (defined as Cmax/Tmax), were calculated for subjects with PK measurements for at least 28 days post-BREYANZI infusion. In addition, the persistence of BREYANZI in the blood was assessed based on the ddPCR assay and separately based on the flow cytometry assay.

Pharmacodynamics, biomarkers, and immunogenicity assessments:

Blood and plasma samples were collected to evaluate the following exploratory pharmacodynamic/biomarker and immunogenicity endpoints:

- incidence of B-cell aplasia and serum immunoglobulins
- C-reactive protein (CRP), ferritin, and other soluble biomarkers
- anti-therapeutic antibody (ATA) assay to detect the presence of serum antibodies that bind to the extracellular region of BREYANZI.

1. Dosing Assessment

A total of 89 (96.7%) subjects in the Safety Analysis Set received BREYANZI. The median total BREYANZI dose was 99.9 x 10^6 cells (range 97.1 to 102.5 x 10^6 cells). The median

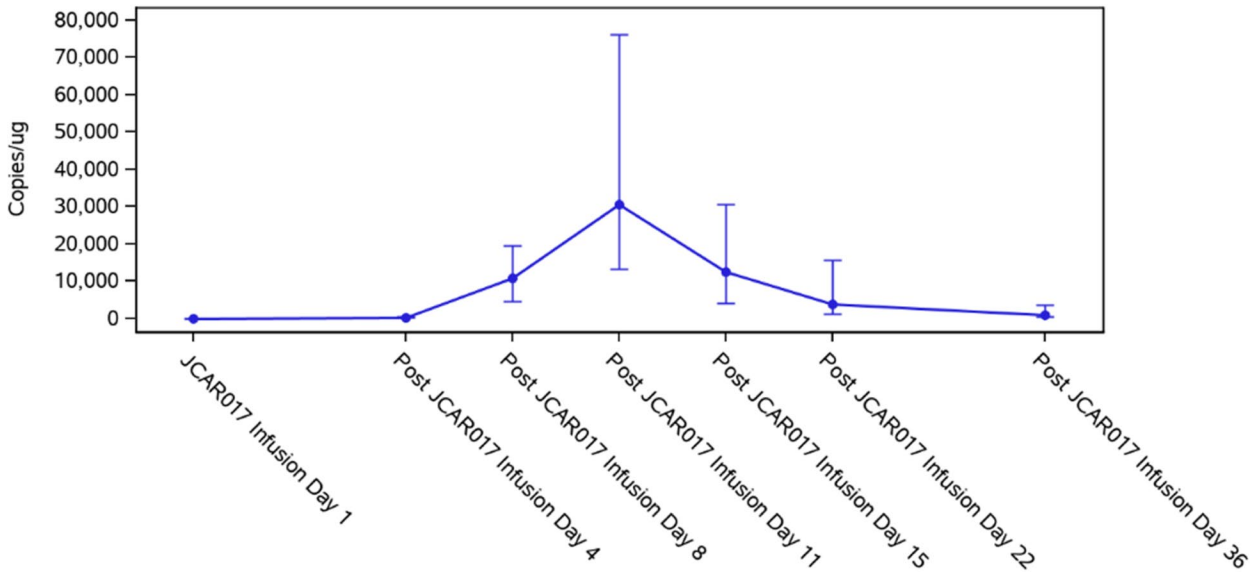
CD8 and CD4 doses were 49.97 x 10^6 cells and 49.89x10^6 cells, respectively. One (1.1%) subject received nonconforming product because the CD4 component purity was out of specifications (OOS).

Reviewer comments: The proposed target dose of BREYANZI is 100 million CAR-positive viable T cells. In the previous dose finding study (#017001) there was no evident dose-exposure and dose-response relationship across the three dose levels (50, 100,150 million cells). For example, there was no significant difference between dose level 2 (100 million cells) vs. dose level 3 (150 million cells) in terms of Tmax and Cmax. The current FDA approved dosing of BREYANZI is 50 to 110 million CAR-positive viable T cells. Overall, experience from previous and current clinical pharmacology studies support the applicant proposed dose of 90-110 million CAR-positive vial T cells.

2. Pharmacokinetics of BREYANZI in peripheral blood

Following infusion, BREYANZI exhibited a rapid expansion followed by a decline up to 35 days in peripheral blood as detected by ddPCR (Figure 1).

Figure 1: Median [Q1, Q3] ddPCR-based BREYANZI Concentrations in Peripheral Blood Time Profiles (PK Analysis Set BREYANZI Arm)



Source: CSR; Figure 14.2.7.1.1

PK parameters based on ddPCR to detect for the BREYANZI transgene vector sequences in blood samples from treated subjects in the BREYANZI arm were like that for subjects from the SOC arm who crossed over to receive BREYANZI (Table 1). The median Tmax occurred 10 days after infusion in both treated subjects in the BREYANZI arm and subjects from the SOC arm who crossed over to receive BREYANZI.

A good correlation between ddPCR (transgene) and flow cytometry (CD3+ EGFRt+ T cell) PK parameters was observed in the BREYANZI arm for Cmax and AUC (0-28), with a correlation coefficient of 0.76 and 0.83, respectively. A weak correlation for Tmax between ddPCR and flow cytometry (correlation coefficient of 0.21) was observed. However, this result should be interpreted with caution because there was no flow cytometry-based PK data on post-infusion day 11 in the BREYANZI arm, when the peak was observed for ddPCR-based PK.

Persistence of BREYANZI transgene in the peripheral blood is defined as a transgene count greater than or equal to the limit of detection (LOD) of 40 copies/µg. The BREYANZI transgene was detected in 61 out of 67 subjects (91%) at day 36 post-infusion and 6 out of 17 subjects (35.3%) at month 11 post-infusion. BREYANZI transgene was not detected in any subjects at month 17 in the BREYANZI arm (n=6 subjects).

Reviewer comments: The cellular kinetics follow expected pattern of initial expansion and persistence. The PK results indicate comparability of Cmax, Tmax and AUC between subjects who crossed over from SOC and BREYANZI arm. Thus, from this PK comparability assessment, we may infer no impact of prior therapy (i.e., HDCT and HSCT as part of SOC) on CAR T cells exposure parameters (Cmax and AUC).

The PK analysis of subgroup showed no apparent differences by age (< 65 versus ≥ 65 to < 75 years old), region (United States, Europe versus Japan), and baseline sum of product of perpendicular diameters (SPD ≥ 50 versus < 50 cm^2). A potential association was observed between higher Cmax and female sex (Cmax=17656.18 copies/µg in male subjects versus Cmax= 45492.20 copies/µg in female subjects, p = 0.0411); however, the IQRs overlapped for female and male subjects.

Subjects treated with tocilizumab (n = 18) had a 2.29-fold and 4.01-fold higher median transgene Cmax and AUC (0-28), respectively, compared to subjects who did not receive tocilizumab (n = 65). Median transgene Tmax of subjects with and without tocilizumab was 9.5 and 10.0 days, respectively. Subjects who received corticosteroids (n = 12) had a 3.49-fold and 3.86-fold higher median transgene Cmax and AUC (0-28), respectively, compared with subjects who did not receive corticosteroids (n = 71). Median transgene Tmax of subjects with and without corticosteroids was 9.5 and 10.0 days, respectively.

Reviewer comments: The relationship between tocilizumab and/or corticosteroids exposure versus PK parameters (Cmax and AUC) are expected based on previous experience. However, the results of PK subgroup analysis based on demographics and product attributes are inconsistent with previous findings. For example, in previous study (#017001) age and SPD were associated with cell expansion. In the present study, both age and SPD have no impact on PK parameters while a trend for potential impact of sex on Cmax was noted. Some of the factors that contribute for the observed discrepancies on the impact of demographics and product related factors on the PK parameters are:

- **Sample size for subgroup analysis. For example, in study (#017001) subjects < 65 years old (N=142) had a 3.06-fold and 2.30-fold higher median Cmax and AUC0-28d, respectively, compared to subjects ≥ 65 years old (N=96). In the current study no effect of age on PK parameters but the sample size was small (N= 53 subjects < 65 years old and N=30 subjects >65 years old).**
- **Dose range. In the previous study (#017001) three dose levels (50, 100,150 million cells) were evaluated while only one dose level (100 million cells) was evaluated in this study.**

Table 1: Summary of BREYANZI Pharmacokinetic Parameters (ddPCR PK Analysis Set)

	Statistic	$AUC_{(0-28)}$ (day*copies/µg)	Cmax (copies/µg)	Tmax (day)
Arm B (N = 87)	n	83	83	83
	Median	270345.09	33349.23	10.0
	Q1, Q3	111550.33, 793715.95	13872.86, 95617.53	9.0, 11.0
	Min, Max	5116.0, 4836898.5	549.0, 475990.7	6, 22
	Geometric mean (geometric CV%)	291943.747 (215.5)	35469.2 (205.2)	-
Arm A post-cross Over (N = 45)	n	38	38	38
	Median	305969.92	35894.73	10.0
	Q1, Q3	145995.19, 788819.00	12603.48, 71776.68	8.0, 13.0
	Min, Max	2139.7, 5999080.3	143.1, 454083.5	6, 28
	Geometric mean (geometric CV%)	318654.555 (265.3)	30675.4 (261.3)	-

Source: CSR; Table 14.2.2.1.2.1

3. Pharmacodynamic Assessment

B-cell aplasia:

The incidence of B-cell aplasia (defined as < 3% of CD19+ B cells in peripheral blood lymphocytes) was assessed for both the BREYANZI arm and SOC post-cross over arms. An increase in the proportion of subjects with B-cell aplasia was observed from 80.7% of subjects at screening to 95.9% of subjects at Day 29, which remained elevated through up to 2 months post-infusion, in the BREYANZI arm. In the SOC post-cross over arm, 97.5% of subjects at pre-lymphodepletion and 100% of subjects at Month 2 had B-cell aplasia. No difference in B-cell aplasia was observed between the BREYANZI arm and SOC post-cross over arm.

Serum IgG:

The level of IgG and incidence of hypogammaglobulinemia (defined as IgG < 500 mg/dL) was evaluated for the BREYANZI arm. The percentage of subjects with hypogammaglobulinemia was 31.5% (28 of 89 subjects) at baseline and increased numerically at Month 9 to 58.6% (20 of 46 subjects), followed by a decrease to 50% (5 of 10 subjects) by Month 18. The analysis of serum IgG levels did not take into account

potential confounding by the administration of IVIG for the treatment of hypogammaglobulinemia.

Soluble biomarkers:

The changes from baseline in cytokine and chemokine levels were analyzed following BREYANZI infusion. A trend for increased level of cytokines such as IL-6 and IFN-gamma after BREYANZI infusion was observed. The peak levels for IL-6 and IFN-gamma were observed within 10 days after BREYANZI infusion and returned to baseline levels by 35 days.

The median baseline level of C-reactive protein (CRP) was 5.31 mg/L and increased to 9.3 mg/L at day 36 following BREYANZI infusion. From days 53 to 120, the CRP level varied between 1.9 to 3.0 mg/L.

4. Exposure-Response Relationships

Exposure-Efficacy Analysis:

Logistic regressions analysis was performed to evaluate the relationship between disease response (BOR, EFS, PFS and DoR) and exposure parameters of BREYANZI determined by ddPCR (Cmax and AUC0-28d). No apparent relationships were observed between transgene PK parameters and any efficacy endpoints (BOR, EFS, PFS and DoR).

Reviewer comments: The exposure-efficacy analysis did not reveal statistically significant difference between responder and non-responder subjects. Although statistically not significant, Cmax and AUC values are higher in non-responders vs responders. In this study, the median Cmax in responders (N=76) and non-responders (N=7) was 33,285 copies/µg and 95,618 copies/µg, respectively. This finding is somewhat unexpected based on the experience from the previous study (#017001) that showed responders (N=135) had a 2.3-fold higher median Cmax than non-responders (N=37) (35,335 vs. 15,527 copies/µg). This discrepancy could be due to the difference in patient population, limited number of non-responders, dose range and high inter-individual PK variability.

Exposure-Safety Analysis:

A potential association was observed between higher transgene Cmax or AUC(0-28d) and higher incidence of any grade CRS (Table 2). A similar potential association was observed between higher transgene or AUC(0-28d) and higher incidence of any grade investigator-identified neurologic toxicity (iiNT). The relationship between PK parameters and grade ≥ 3 CRS or iiNT was not assessed because the number of subjects with grade ≥ 3 CRS (n = 1) or iiNT (n=4) was small.

Table 2: Relationship between Exposure parameters and cytokine release syndrome (CRS)

	Yes, CRS, n=41	**No, CRS, n=42**	**p-value**
Cmax, median (Q1, Q3)	49731 (16840,151636)	27112.54 (13064,55286)	0.02
AUC0-28d, median (Q1, Q3)	347981 (122372,1039230)	190687 (80791,459856)	0.03

Source: CSR; Table 14.2.2.2.3.3.3

Reviewer comments: Exposure-safety (CRS) analysis was conducted using balanced sample size (i.e., No CRS, n= 42 and CRS, n=41), and the exposure-CRS analysis showed statistically significant increase in CRS with higher exposure parameters (i.e., Cmax and AUC). This result is consistent with previous finding from study #017001.

5. Immunogenicity

In subject without pre-existing antibodies, development of antibodies after first infusion of BREYANZI is considered treatment-induced. In subject with pre-existing antibodies, an increased level of antibodies after first infusion of BREYANZI is considered treatment-boosted. Incidence of anti-therapeutic antibodies (ATA) is defined as the percentage of

subjects with treatment-induced or treatment-boosted antibodies that bind to BREYANZI. In the BREYANZI arm, the prevalence and incidence of ATA was 1.1% (1 of 89 subjects). In subjects from the SOC arm who crossed-over to receive BREYANZI, the prevalence of ATA was 2.2% (1 of 46 subjects) and the incidence of ATA was 0 (0 of 46 subjects).

The subject who had a pre-existing ATA in the BREYANZI arm achieved a BOR of a CR and did not experience any CRS or iiNT. Cmax and AUC (0-28) by ddPCR of this subject were 6983.2 copies/µg and 45503.97 day*copies/µg, respectively, which were lower than the median values of the overall BREYANZI arm population (median Cmax= 33349 copies/ug, and median AUC= 270345 dayxcopies/ug, n=83).

Reviewer comments: The patient with pre-existing ATA appears to have lower Cmax (79%) and AUC0-28 (83%). This decrease in exposure appears to be not relevant considering the higher variability in cellular expansion parameters and no significant correlation between exposure and efficacy. Based on the current limited data, it is difficult to make any conclusion on the relationship between ATA status and efficacy, safety or pharmacokinetics.

6.2 Study 017006: *A Phase 2 study of Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-cell NHL (017006)*

The primary objective of the study was to evaluate the antitumor activity of BREYANZI in adult subjects with LBCL who are ineligible for HSCT. The clinical pharmacology objective is to characterize the PK profile of BREYANZI.

Overall Study Design and Plan:

Leukapheresis was performed on each subject to collect enough PBMCs for the production of the BREYANZI investigational product. All subjects were assigned to a single BREYANZI dose of 100 × 10^6 CAR+ T cells (50 × 10^6 $CD8^+$ CAR^+ T cells and 50 × 10^6 $CD4^+$ CAR^+ T cells), administered intravenous (IV) on Day 1 (between 2 and 7 days following the completion of lymphodepleting chemotherapy). Overall, 93 subjects were screened, 80 deemed eligible, 63 received lymphodepleting chemotherapy, and 61 received BREYANZI (one received nonconforming product).

Pharmacokinetic Assessments:

The PK profile of BREYANZI was characterized using quantitative polymerase chain reaction (qPCR) and supportive PK analysis was performed by flowcytometric method. Blood samples for cellular kinetics analysis were collected as follows:

- Days 1 (pre-infusion)
- Post-infusion at days 4, 8, 11, 15, 22, 29,
- Post-infusion months 2, 3, 6, 9, 12, 15, 18 and 24 (EOS)

Pharmacodynamics, biomarkers and immunogenicity assessments:

Peripheral blood and plasma were collected to evaluate the following exploratory pharmacodynamic/biomarker endpoints:

- the incidence of B-cell aplasia and serum immunoglobulins
- C-reactive protein (CRP), ferritin, and other soluble biomarkers

Immune responses to BREYANZI were evaluated with an anti-therapeutic antibody (ATA) assay to detect the presence of serum antibodies that bind to the extracellular region of BREYANZI.

1. **Pharmacokinetics of BREYANZI in peripheral blood**

Pharmacokinetic parameters based on qPCR detection of transgene vector sequences in peripheral blood samples are presented in Table 3. A good correlation between qPCR (transgene) and flow cytometry (CD3+ EGFRt+ T cell) PK parameters was observed for Cmax, Tmax, and AUC (0-28), with a correlation coefficient of >0.79.

The persistence of BREYANZI transgene in the peripheral blood is defined as a transgene count greater than or equal to the LOD of 5 copies/reaction. The BREYANZI transgene level was detected in 94% (47 out of 50 subjects) at Day 29 and 60% (9 out of 15 sujects) at Day 365.

The persistence of BREYANZI transgene was observed up to Day 545 in two out of three evaluated (33%). At Day 730, transgene level was not detected in none of the two subjects where transgene level is evaluated.

The PK analysis of subgroup showed no apparent differences by age (< 65 versus ≥ 65 to < 75 years old), sex, and baseline SPD (≥ 50 versus < 50 cm^2).

Subjects treated with tocilizumab (n = 12) had a 1.19-fold and 1.13-fold higher median transgene Cmax and AUC (0-28), respectively, compared to subjects who did not receive tocilizumab (n = 43). Median transgene Tmax of subjects with and without tocilizumab was 8.0 and 10.0 days, respectively.

Subjects who received corticosteroids (n = 11) had a 1.23-fold and 1.19-fold higher median transgene Cmax and AUC (0-28), respectively, compared with subjects who did not receive corticosteroids (n = 44). Median transgene Tmax of subjects with and without corticosteroids was 7.0 and 10.0 days, respectively.

Reviewer comments: The cellular kinetics follow expected pattern of initial expansion and persistence. There is a good correlation (correlation coefficient >0.79) for exposure parameters derived from qPCR and flow cytometry, but the

qPCR method is more sensitive and appropriate to employ as a primary assay for PK assessment.

Table 3: Summary of BREYANZI Pharmacokinetic Parameters in Peripheral Blood by qPCR - qPCR Pharmacokinetic Analysis Set

Statistic	AUC (0-28) (day*copies/µg)	Cmax (copies/µg)	Tmax (day)
n	55	55	55
Median	222758.1	23000.0	10.0
Q1, Q3	92045.8, 487246.5	12012.0, 52628.0	8.0, 14.0
Min, Max	2376, 2093636	275.0, 383590.0	6, 22
Geometric mean (geometric CV%)	178930.7 (228.4)	22516.3 (237.4)	-

Source: Study 017006 Clin Pharm Report; Table 6.1.2-1

2. Pharmacodynamics: B-cell Aplasia and serum immunoglobulins

An increase in the proportion of subjects with B-cell aplasia was observed from 80% of subjects at baseline (48 out of 60) to 100% of subjects at Day 29 (53 out of 53) and 95.2% at Day 90 (40 out of 42). The proportion of subjects with B-cell aplasia returned to 80 % at Day 180 (24 out of 30).

The percentage of subjects with hypogammaglobulinemia (defined as IgG < 500 mg/dL) was 34.4% at baseline (21 out of 61 subjects), which increased to 57.6% at Day 29 (34 of 59 subjects) and remain elevated through Day 365 (50%, 8 of 16 subjects).

3. Immunogenicity Assessments

At baseline none of the 51 subjects have anti-therapeutic antibodies (ATA). After treatment one subject (2%) developed anti-therapeutic antibodies (1 of 49 subjects). The small sample size did not allow to assess potential relationship of anti-therapeutic antibodies with efficacy, safety, or PK. The subject who had a treatment-induced ATA achieved a BOR of a CR and did not experience any CRS or iiNT. Cmax and AUC (0-28) by qPCR of this subject were 54874 copies/µg and 231992 day*copies/µg, respectively, which were higher than the median values of overall population (Cmax=23000 copies/µg and AUC=222758 day*copies/µg)

Reviewer comments: The subject who had treatment induced ATA had higher Cmax (138%) and AUC (4 %). Based on the limited data, it is difficult to make any conclusion on the relationship between ATA status and efficacy, safety or pharmacokinetics.

4. Exposure-Response Relationships

Exposure-Efficacy Analysis:

Logistic regressions analysis was performed to evaluate the relationship between disease response (BOR) and exposure parameters of BREYANZI determined by qPCR (Cmax and AUC0-28d). No apparent relationships were observed between transgene PK parameters and any efficacy endpoints (BOR).

Exposure-Safety Analysis:

No apparent statistically significant relationships were observed between transgene PK parameters (Cmax and AUC) and any grade CRS. A potential association was observed between earlier transgene Tmax and higher incidence of any grade CRS. This statistical difference should be interpreted carefully as the difference in median Tmax between responder and non-responder was only 1 day. The relationship between PK parameters and Grade ≥ 3 CRS was not assessed because the number of subjects with Grade ≥ 3CRS (n = 1) was less than 5. A potential association was observed between higher transgene Cmax and higher incidence of any grade iiNT (p=0.0297).

Reviewer comments: The exposure-efficacy did not reveal statistically significant difference between responder and non-responder subjects. Also, no exposure-CRS effect was demonstrated other than very marginal difference in Tmax. However, previous studies showed clear relationship between exposure and CRS. This discrepancy could be due to the difference in patient population, sample size, dose range and bioassay.

5. Comparison Clinical Pharmacology Results Across Studies

For clinical pharmacology comparative evaluation, the following three studies were included:

- Study (#017001): considered a reference study as it was previously reviewed and approved
- Current studies (#BCM-003 and #017006): are proposed to support indication of 2L LBCL (second-line treatment of relapsed or refractory (R/R) large B-cell lymphoma)

The study design, sample size, prior treatment, target dose, and bioassay of these three studies are summarized in Table 4. The difference in study design and relevant PK related assessments preclude direct comparison of clinical pharmacology results from #BCM-003 with the other two studies. Thus, clinical pharmacology comparative evaluation was performed between the two relevant studies (#017006 vs #017001) and summarized as follows:

- No apparent differences in BREYANZI Cmax, Tmax and AUC based on qPCR method were noted between 2L LBCL (Study 017006) and 3L+ LBCL (Study 017001, Table 5).
- No apparent difference in BREYANZI persistence was noted until Day 365 (i.e., 1-year after infusion) between # 017006) and # 017001 (Table 2). The persistence data indicate that BREYANZI can be detected in at least 59% of subjects 1-year after infusion (Table 5).
- No apparent difference in B-cell aplasia was noted between # 017006 and # 017001
- In 3L+ LBCL (# 017001), higher transgene Cmax and AUC (0-28) were associated with a higher overall response and complete response rate, and a higher incidence of any grade CRS, any grade iiNT, and Grade ≥ 3 iiNT.
- In 2L transplant-noneligible (TNE) LBCL (#017006), a potential association was observed between earlier transgene Tmax and CR, and higher Cmax and longer PFS. No other apparent relationships were observed between transgene PK parameters and efficacy endpoints. A potential association was observed between earlier transgene Tmax and higher incidence of any grade CRS and between higher transgene Cmax and higher incidence of any grade iiNT. The frequency of

Grade ≥ 3 CRS and iiNT was too low to assess any potential relationship with these events.

Reviewer comments: Overall the PK results are comparable between studies #17006 and #017001. Some discrepancy in the results of exposure-response analysis could be due to the difference in patient population, sample size and dose range as summarized in Table 4.

Table 4: Characteristics of Studies 017001, BCM-003, and 017006

	#017001(DLBCL cohort)	**#BCM-003**	**#017006**
Study Design	Single-arm, Phase 1	Randomized, 2-arm (BREYANZI vs SOC)	Single-arm, Phase 2
Study Sample Size (ITT population)	n=287 subjects	n=92 in SOC arm & n=92 in BREYANZI arm	n=74 subjects
Study Population	Adults with relapsed or refractory LBCL **after at least 2 systemic therapies**	Adults with relapsed or refractory LBCL **after first line (1L) immunotherapy**	Adults with relapsed or refractory LBCL **after first line (1L) immunotherapy**
Prior Treatment	≥ 2 systemic lines of therapy, including CD20 mAb and anthracycline	CD20 mAb and anthracycline-containing 1 L therapy	CD20 mAb and anthracycline-containing 1 L therapy
Target BREYANZI Dose	$50x10^6$, $100x10^6$ & $50x10^6$ CAR T cells	$100x10^6$ CAR T cells	$100x10^6$ CAR T cells
Primary Bioassay Method for PK Assessment	qPCR	ddPCR	qPCR

Source: Compiled by Reviewer from clinical/clinical pharmacology reports

Table 5: **Summary of BREYANZI Transgene Pharmacokinetic Parameters by Studies 17006 and 017001**

	#017001(DLBCL cohort) **N=238[a]**	**#017006** **N=55[a]**
Cmax (copies/µg)	23964 (8159, 78748)	23000 (12012, 52628)
Tmax(day)	12 (10, 15)	10 (8, 14)
AUC (0-28) (day*copies/µg)	214283 (77282, 689752)	222758 (2376, 2093636)
Persistence (% subjects with detectable transgene)	Day 29: 232/236 (98%) Day 180: 58/88 (66%) Day 365: 22/37 (59%) Day 730: 3/8 (38%)	Day 29: 47/50 (94%) Day 180: 20/31 (65%) Day 365: 9/15 (60%) Day 730: 0/2 (0%)

[a] Number of subjects with PK parameters. Median (interquartile Q1 & Q3) values are displayed

Source: CSR,Table 3.1.1-1; Module 2.7.2