BLA Clinical Review Memorandum

Application Type	Original BLA
STN	125714/0
CBER Received Date	December 18, 2019
PDUFA Goal Date	November 16, 2020
Division / Office	DCEPT/OTAT DHM II/OCE
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Megha Kaushal, MD (Efficacy) Kavita Natrajan, MD (Safety)
Review Completion Date / Stamped Date	11/13/2020
Supervisory Concurrence	Yvette Kasamon, MD Bindu George, MD Marc Theoret, MD
Applicant	Juno Therapeutics
Established Name	Lisocabtagene maraleucel (JCAR017)
(Proposed) Trade Name	BREYANZI
Pharmacologic Class	CD19- directed, genetically modified autologous T cell immunotherapy
Formulation(s), including Adjuvants, etc.	75% Cryostor® CS10 [containing 7.5% dimethylsulfoxide], 24% Multiple Electrolytes for Injection, Type 1, 1% of 25% albumin (human)
Dosage Form(s) and Route(s) of Administration	Intravenous
Dosing Regimen	Single dose containing 50 to 110 $x10^6$ CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components) by IV infusion and preceded by fludarabine and cyclophosphamide chemotherapy for lymphodepletion
Indication(s) and Intended Population(s)	Proposed: Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies. Limitation of Use: Not indicated for the treatment of patients with primary central nervous system lymphoma Recommended: 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. Limitations of use: Not indicated for the treatment of patients with primary central nervous system lymphoma.
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE adverse event
AESI adverse event of special interest
Allo allogeneic
AR adverse reaction
Auto autologous
BLA biologics license application
BOR best overall response
CAR chimeric antigen receptor
CMC chemistry, manufacturing and controls
CI confidence interval
CNS central nervous system
CR complete remission
CRS cytokine release syndrome
CSF cerebrospinal fluid
CSR clinical study report
CTCAE common terminology criteria for adverse events
DLBCL diffuse large B-cell lymphoma
DLT dose-limiting toxicity
DOR duration of response
eCTD electronic common technical document
ECOG eastern cooperative oncology group
EEG electroencephalogram
ETASU elements to assure safe use
FAS full analysis set
FDA food and drug administration
FL follicular lymphoma
HLH/MAS hemophagocytic lymphohistiocytosis/macrophage activation syndrome
HSCT hematopoietic stem cell transplantation
IND investigational new drug application
IPI International Prognostic Index
ISS integrated summary of safety
IQR interquartile range
IRC independent review committee
IR information request
LTFU long-term follow up
MedDRA medical dictionary for regulatory activities

mITT modified intention-to-treat
MMSE mini mental status exam
NE not evaluable, not estimable
NESI neurotoxicity events of special interest
NHL non-Hodgkin lymphoma
NT neurologic toxicity
ORR objective response rate
OS overall survival
PD progressive disease
PFS progression-free survival
PI prescribing information/package insert
PK/PD pharmacokinetics/pharmacodynamics
PREA pediatric research equity act
PR partial remission
PS performance status
PT preferred term
RCR replication competent retrovirus
REMS risk evaluation and mitigation strategy
SAE serious adverse event
SAP statistical analysis plan
SCT stem cell transplantation
SD stable disease
SOC system organ class
SCE summary of clinical efficacy
SCS summary of clinical safety
SPD sum of the products of greatest diameter
TEAE treatment-emergent adverse event

1. EXECUTIVE SUMMARY

The clinical review team recommends regular approval of lisocabtagene maraleucel (also known as JCAR017 or BREYANZI) 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. JCAR017 is not indicated for the treatment of patients with primary central nervous system lymphoma.

JCAR017 is a CD19-directed genetically modified autologous cellular immunotherapy consisting of autologous T cells that have been transduced with a lentiviral vector encoding an anti-CD19, *CD28/4-1BB* chimeric antigen receptor (CAR). The recommended regimen is a single dose of JCAR017, with a dose range of 50-110 $x10^6$ viable CAR T cells with a 1:1 CD4/CD8 ratio, administered by IV infusion and preceded by fludarabine and cyclophosphamide conditioning for lymphodepletion. Efficacy and safety are based on Study 017001 (TRANSCEND), a single-arm, open label, multicenter study that evaluated JCAR017, preceded by conditioning chemotherapy, in adults with relapsed or refractory large B cell lymphoma.

Efficacy

The efficacy of JCAR017 is based on complete response (CR) rate and duration of response (DOR) by independent review committee (IRC) assessment in Study 017001,

which enrolled adults with relapsed or refractory, *de novo* or transformed large B-cell lymphoma after two or more lines of systemic therapy. Of 344 subjects who underwent leukapheresis, 269 (78%) received JCAR017, and 256 were evaluable for efficacy. The median number of prior systemic therapies for efficacy-evaluable subjects was 3 (range:1-8). The majority of evaluable subjects (192/256; 75%) received the study drug at the recommended dose schedule. In these 192 subjects, the overall response rate (ORR) according to Lugano criteria was 73% (95% confidence interval [CI]: 67%, 80%) with a CR rate of 54% (95% CI: 46%, 61%); median time to first response was one month. Of the 141 subjects who achieved an objective response, 57.1% maintained response for at least 6 months and 52.8% maintained a response for at least 12 months. The estimated median was not reached in patients who achieved CR. Study 017001 met the study objective that ORR was statistically significantly greater than the pre-specified null hypothesis rate of 40%.

Safety

Study 017001 served as the primary source of safety data and included a total of 268 subjects with large B-cell lymphoma treated with JCAR017 across 3 main dose regimens (single dose levels 1, 2 and 3 with planned dose of 50×10^6, 100×10^6 and 150×10^6 CAR-T cells respectively). Grade 3 or higher adverse reactions of interest included cytokine release syndrome (4%), neurologic toxicity (12%), infections including febrile neutropenia (19%), and prolonged cytopenias (31%). Non-fatal cerebral edema and 3 deaths from encephalopathy including events attributed mainly to Fludarabine in the lymphodepleting chemotherapy occurred. No new safety signals were identified in the 120-day safety update report.

During study 017001, life-threatening adverse reactions attributed to JCAR017 were mitigated by mandated site and investigator training, careful site selection and monitoring, and instructions for early detection and management of the most serious complications. The life-threatening and fatal adverse reactions warrant warnings and precautions in the USPI, including a boxed warning for cytokine release syndrome (CRS) and neurologic toxicity (NT), and a risk evaluation and mitigation strategy (REMS). FDA determined that a REMS with elements to assure safe use (ETASU) is necessary for JCAR017. The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies, with emphasis on early recognition and treatment of CRS and neurologic toxicity.

Long-term safety after treatment with JCAR017, particularly regarding the risk of insertional mutagenesis- related secondary malignancies, remains a concern due to the limited duration of follow-up. Therefore, a post-marketing requirement (PMR) safety study is warranted. The applicant agreed to conduct an observational registry study that will collect safety information on a minimum of 1000 patients treated with the marketed product, including key early adverse reactions and follow-up for 15 years for detection and evaluation of second malignancies. No routine collection of samples to test for competent lentiviral replication is planned as part of this study.

In summary, Study 017001 represents an adequate and well controlled study that demonstrated high response rates and durability of CR rate with an acceptable safety profile. Given the life-threatening nature of the disease in the indicated population, the adverse reactions of CRS and NT, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective. Thus, the overall benefit-risk profile favors regular approval of BREYANZI in patients with R/R large B-cell lymphoma.

Demographic Information: Subgroup Demographics and Analysis Summary

Table 1: Demographic Information

	Leukapheresed set n=344	Treated analysis set n=269	DLBCL Efficacy set n=256
Age (years)			
Mean (STD)	60.0 (13.1)	60.1 (13.3)	60.3 (13.3)
Median (min, max)	62 (18, 86)	63 (18, 86)	63 (18, 86)
Sex n (%)			
Female	122 (35.5%)	95 (35.3%)	87 (34.0%)
Male	222 (64.5%)	174 (64.7%)	169 (66.0%)
Race n (%)			
White	294 (85.5%)	232 (86.2%)	219 (85.5%)
Black or African American	17 (4.9%)	12 (4.5%)	12 (4.7%)
Asian	13 (3.8%)	11 (4.1%)	11 (4.3%)
Other	20 (5.8%)	14 (5.2%)	14 (5.5%)
Ethnicity n (%)			
Hispanic or Latino	34 (9.9%)	26 (9.7%)	24 (9.4%)
Other	310 (90.1%)	243 (90.3%)	232 (90.6%)

Briefly, the leukapheresed set include all subjects who underwent leukapheresis. The treated analysis set includes all subjects who received JCAR017. The DLBCL efficacy set includes subjects who met eligibility criteria of PET positive disease and received JCAR017. Further detail of these populations is described in Section 6.1.10.

1.2 Patient Experience Data

Quality-of-life outcomes were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (Version 3) and the (b) (4)

Reviewer Comment: The Applicant did not seek a labeling claim based on COA data and these data were not incorporated in the PI. The data were not evaluated as part of the application review, given the limitations of COA assessments in uncontrolled, open-label trials. As with time-to-event endpoints, interpretation of patient-reported outcomes is challenging in uncontrolled clinical trials, because it is unclear to what extent the outcomes can be attributed to the treatment effect of the regimen vs. to underlying disease and patient characteristics.

Table 2: Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	1.2
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	

	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.		

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

DLBCL, which comprises 30-40% of NHLs, is fatal if not cured. PMBCL and transformed FL are typically treated along a DLBCL paradigm. Approximately half of all patients with aggressive B-cell NHL have relapsed or refractory (R/R) disease, with an estimated 10-15% of patients with DLBCL having primary refractory disease and an additional 20-30% relapsing after an initial objective response (Chaganti et al 2016). High-grade B-cell lymphomas with aberrations in MYC, BCL2 and/or BCL6 ("double hit" and "triple hit" lymphomas) are associated with an inferior prognosis, even in the newly diagnosed setting (Rosenthal and Younes 2017). Patients with untreated rel/ref aggressive B-cell lymphoma have a median survival of approximately 3-4 months.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Although standard chemoimmunotherapy (R-CHOP) is curative for more than half of patients with newly diagnosed DLBCL, an estimated 20-30% relapse after an initial remission and an estimated 10% have primary refractory disease.[1-3] For first relapse, high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT) is the usual standard provided that the relapse is chemosensitive. However, over 50% of such relapses can be resistant to second-line therapy,[4] typically precluding HSCT, and comorbidities may also preclude HSCT. Outcomes tend to be especially poor with DLBCL that is refractory or relapses early after autologous HSCT.[5-7] In a meta-analysis of over 500 such patients, ORRs to subsequent therapy were 20-30%, CR rates were ≤ 15%, and the median overall survival (OS) was 6 months.[5]

There is no one universal standard for patients with DLBCL after failure of two or more lines of therapy, including patients who are ineligible for, or who relapse despite, HSCT.[1,8] Allogeneic HSCT can produce durable remissions, if not cure, in a subset of patients despite failure of autologous HSCT. However, patients unable to achieve sufficient disease control with salvage therapy are generally not considered for allogeneic HSCT, given the high relapse risk. Other potential barriers to allogeneic HSCT include comorbidities, advanced age, and donor availability.

Two CD19-directed, chimeric antigen receptor (CAR) T cell therapies have been approved for the treatment of large B-cell lymphoma. Axicabtagene ciloleucel (YESCARTA) and Tisagenlecleucel (KYMRIAH) have regular approval for the treatment of adult patients with (R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma (FL), and (for axicabtagene ciloleucel) primary mediastinal large B-cell lymphoma. The basis for approval for these products was complete response rate and duration of response.

Selinexor is a first-in-class, small molecule inhibitor of the nuclear export protein, exportin 1 which has accelerated approval for the treatment of adult patients with R/R DLBCL, NOS, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy.

Polatuzumab in combination with bendamustine and rituximab has accelerated approval for the treatment of adult patients with R/R DLBCL after at least two prior therapies.

Tafasitamab in combination with lenalidomide has accelerated approval for the treatment of adult patients with R/R DLBCL, NOS, including DLBCL arising from low grade lymphoma and who are not eligible for autologous stem cell transplant.

2.3 Safety and Efficacy of Pharmacologically Related Products

Axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah) and brexucabtagene autoleucel (Tecartus) are all commercially available CD19 directed CAR-T cell therapies. Axicabtagene ciloleucel and tisagenlecleucel are approved for the treatment of adult subjects with R/R large cell lymphoma with at least 2 prior lines of systemic therapy with indication for DLBCL NOS, high grade B cell lymphoma and follicular lymphoma; tisagenlecleucel has added indication for PMBCL. Brexucabtagene autoleucel has accelerated approval for the treatment of adult subjects in R/R mantle cell lymphoma.

Cytokine release syndrome (CRS) and neurologic toxicity (NT) are serious adverse events associated with CAR-T therapies. CRS results from massive cytokine and chemokine release when CAR-T cells engage with tumor cells via the targeted antigen and is characterized by a constellation of symptoms (subject can have one or more symptoms with fever being the sine qua non) including fever, chills, hypotension, hypoxia and in severe cases organ damage e.g. renal failure, coagulopathy and death. Management of CRS includes targeting IL-6 (thought to be central to CRS pathophysiology) with an IL-6 antibody-tocilizumab, corticosteroids (general suppression of inflammation) and supportive care e.g. fluids, vasopressors, oxygen, ventilatory support etc.

CAR-T cell associated NT, currently referred to as immune effector cell associated neurotoxicity syndrome (ICANS), may manifest as delirium, encephalopathy, aphasia,

tremor, seizures and cerebral edema. NT is thought to be distinct in pathophysiology from CRS and occurs commonly with or after CRS. Symptoms such as headache are thought to be less specific for NT and are not included in current ICANS grading as are more specific but non-life-threatening symptoms like tremor. Corticosteroids and antiseizure medications (prophylaxis or treatment) form the cornerstone of NT management. tocilizumab or other IL6 blocking agents are given in NT if subjects have concurrent CRS; use in NT alone has raised concern for worsening NT due to higher levels of IL6 in the CSF.[9,10]

In the licensing trial for axicabtagene ciloleucel that included 108 subjects for safety analyses, CRS occurred in 94% (101/108) subjects with grade 3 and higher events in 13% (14/108). Neurologic toxicity occurred in 87% of subjects including grade 3 or higher events in 31% of subjects. CRS occurred in 74% (78/106) subjects in the licensing trial for tisagenlecleucel with grade 3 and higher CRS incidence in 23% of subjects. All grade and grade 3 and higher NT occurred in 58% (62/106) and 18% of subjects respectively. In the ZUMA-2 licensing trial for brexucabtagene autoleucel, all grade and grade 3 and higher CRS occurred in 91% (75/82) and 18% of subjects respectively while all grade and grade 3 and higher NT occurred in 81% and 37% respectively.

Cross trial comparisons of safety are difficult given that study populations may differ despite similar diagnosis and evolving understanding in the pathophysiology and management of CRS and NT.

Given risk of life threatening and fatal toxicities with CRS and NT, all 3 commercially available products have a black-box warning for these toxicities and are available only with a restricted program called Risk Evaluation and Mitigation Strategy (REMS) in place.

In addition to the above risks, CAR-T cell therapy using retroviral or lentiviral vectors carries risk for insertional mutagenesis and thus secondary malignancies in its recipients. Therefore, all products have a pre- and post-marketing requirement of 15-year follow up for long term adverse events.

Efficacy for large B cell lymphoma was established on the basis of complete remission (CR) rate and duration of response (DOR) for the CAR-T products above.
For Yescarta, the ORR rate was 72% with a CR rate of 51%. The median DOR was 9.2 months overall, and was not reached for patients achieving CR. For Kymriah, the ORR rate was 50% with a CR rate of 32%. The median DOR was not estimable.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

None. JCAR017 is a new immunotherapy and has not been marketed in other countries.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

26 June 2015 Study 017001 under new IND 16506 allowed to proceed

27 April 2016 Orphan drug designation (ODD) granted to JCAR017 for the treatment of DLBCL (designation 15-5161). Per the Pediatric Research Equity Act (PREA) and 21 Code of Federal Regulations (CFR) 314.55(d), ODD products are exempt from pediatric study requirements. Because of ODD, the applicant did not include a pediatric assessment in this biologics license application (BLA) for JCAR017.

31 October 2016 Type C meeting. Development of the JCAR017 clinical program including plan in relapsed/refractory large B-cell NHL, acceptability of study 01701 as the pivotal trial to support full approval, bridging strategy to support major manufacturing process changes and trail design for CLL/SLL or Richter's transformation discussed.

15 December 2016 Breakthrough therapy designation (BTD) granted to JCAR017 for the treatment of patients with relapsed/refractory aggressive large B-cell NHL, including DLBCL NOS-de novo or transformed from indolent lymphoma, PMBCL or grade 3B follicular lymphoma.

23 May 2017 Type B meeting discussion for nonclinical and clinical pharmacology programs to support a BLA, statistical analysis plan (SAP) for study 017001, CMC strategy for analytical comparability between pre-and post-change drug product.

07 September 2017 Orphan drug designation (ODD) granted to JCAR017 for the treatment of follicular lymphoma (designation 17-6005).

20 October 2017 RMAT designation granted to JCAR017 for the treatment of patients with relapsed/refractory aggressive large B-cell NHL, including DLBCL NOS-de novo or transformed from indolent lymphoma, PMBCL or grade 3B follicular lymphoma.

11 December 2017 Deficiency letter for BB-MF (b) (4) -additional information requested for LV vector test methods; advice for stability studies and requirements for acceptance criteria for release tests provided

18 December 2017 Type B meeting for CMC strategies intended to support JCAR017 licensure with advice on drug product specifications, drug process validation and facilities

20 March 2018 Type B meeting for i) plan on pooling safety and efficacy data for recommended dose (100 x 10^6 CAR+T cells) with conforming product across various manufacturing versions ii) format and clinical contents of BLA submission that included requirements for adequate follow up, elements of separate CRS dataset, eCRFs and eligibility for efficacy analysis iii) non-clinical comments

21 June 2018 Type B meeting: i) CMC strategy for drug product specifications, validation and dose calculation to support JCAR017 licensure ii) Format and content of Quality section of BLA

01 May 2018 Deficiency letter BB-MF (b) (4) for additional information for LV vector comparability and JCAR017 comparability

12 July 2018 OOD for treatment of PMBCL granted (#DRU-2018-6440)

05 September 2018 BREYANZI accepted as proprietary name

14 September 2018 Type B Written Responses Only (WRO) meeting-clarification on format and content requirements of clinical and data elements of BLA submission that included i) required narratives for CRS, NT and other AESI ii) manufacturing version and actual dose administered data submission iii) disease histologies to be included for

efficacy iv) safety population to be included in the datasets v) efficacy assessments vi) retreatment vii) flagging datasets for NT, CRS viii) exposure data for safety and efficacy

20 November 2018 Teleconference to discuss strategy for LV vector comparability plan and vector potency testing strategy

03 May 2019 Teleconference on Module 3 BLA CD4/CD8 content organization and (b) (4) acceptance criteria

August 5 2019 Pre-BLA meeting with key issues discussed as follows: i) content and format of DOVER and CLOVER reports with dose administered, dose ranges across manufacturing versions and their impact on clinical outcomes ii) amendment within 30 days of original BLA submission to provide follow up on duration or response iii) dose being a review issue iv) PET and CT integration for disease response assessment v) Pooling and analyses strategy of integrated summary of safety (ISS) and 90 day safety update vi) narratives for retreatment vii) SAP viii) clinical pharmacology and non-clinical package adequacy ix) Preliminary PVP and REMS plan x) Rolling BLA submission xi) CMC issues on acceptance criteria for drug product initial commercial specification, viability, (b) (4), potency, shelf life xi) inspection timelines xii) draft JCAR017 container and carton labels

30 September 2019 Original BLA submission; 1st component of rolling submission (M2, M4- Non-clinical study reports)

30 October 2019 2nd component of BLA rolling submission (M1, M2 and M5-clinical)

18 December 2019 3rd and final component of BLA rolling submission (M1 updated USPI and M1.6.3, M1-clinical information amendment, M3 Quality, M5 datasets, IRC eCRFs, clinical efficacy narratives, supporting documentation for progressive disease findings). Request for priority review designation submitted

18 February 2020 BREYANZI PNR review accepted

05 May 2020 Major amendment issued for substantial new manufacturing and facility information that needed to be reviewed. PDUFA goal data pushed back to November 16, 2020

2.6 Other Relevant Background Information

Six protocol amendments were filed to study 017001 prior to the data cutoff of April 12, 2019. A summary of major changes associated with each amendment is provided below.

Amendment 1 (September 2015)
i) Changes to eligibility criteria for renal function ii) information for additional cycles for JCAR017 treatment in subjects who achieved a response iii) local cytokine analysis was made optional iv) consultation with Sponsor in the event that LDC was delayed > 14 days and additional dosing recommendations for LDC v) details on number of subjects for the regimen finding part of the study, number of subjects in each disease cohort vi) updated simulation report for hierarchical dose-response model, results and operating characteristics based on efficacy data across disease cohorts

Amendment 2 (March 2016)
i) Second group of subjects at dose level 2, single (DL2S) and dose level 2, two-dose (DL2D) if safety established in dose level 1, single (DL1S) ii) Increase in sample size from 70 to 90 subjects iii) clinical data from subjects with ALL and NHL treated with JCAR017 in study (NCT#01865617) updated iv) Bayesian adaptive design for dose cohort 2 added

Amendment 3 (June 2016)
i) 3rd higher dose cohort of 150 x 10^6 CAR+T cells added ii) dose expansion at dose levels following safety and efficacy in dose-finding part allowed iii) efficacy changed from secondary to primary endpoint iv) updated sample size and SAP based on clinical changes v) safety review committee added vi) IRC efficacy assessment added vii) follow up increased to 2 years viii) eligibility criteria changed to exclude 2nd line transplant ineligible subjects, allow PMBCL diagnosis and require tumor biopsy tissue to be available at baseline

Amendment 4 (January 2017)
i) define the primary analysis set (PAS) for efficacy ii) dose confirmation group added with requirement to reach at least 100 subjects with DLBCL iii) prespecified interim analyses added after 50 subjects in PAS had been followed for at least 3 months iv) subjects with secondary CNS lymphoma, chemo-refractory DLBCL allowed v) CR, DOR changed from primary to secondary endpoints; PFS added as secondary endpoint vi) subgroup analyses for safety and efficacy added vii) CRS and other toxicity management updated viii) reporting period for AEs changed from 30 days to 90 days

Amendment 5 (August 2017)
i) safety and futility boundaries for dose confirmation group added ii) timing of prespecified analysis amended to include minimum of 75 subjects in PAS be treated at a dose regimen and the first 50 subjects in the dose confirmation group have been followed for at least 3 months and 20 subjects followed for at least 6 months iii) subjects with ECOG PS 2 excluded iv) CRS and NT management updated especially for Grade 1 and 2 CRS v) PAS update to exclude FL grade 3B, DLBCL transformed from other histologies, subjects with ECOG 2 PS and prior allogeneic stem cell transplant

Amendment 6 (April 2018)
i) Implementation of larger windows around day 180 and day 270 imaging ii) changes in Fludarabine dosing for renal insufficiency iii) PK objective changed from primary to secondary objective iv) removal of additional cycles of JCAR017 for those with a response < CR v) updated CRS and NT management vi) guidance on clinical stability prior to JCAr017 administration

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The overall submission quality and content were acceptable. Inadequacies, including different sample size for efficacy assessments, insufficient follow up for response duration, and dataset errors and omissions, were addressed through multiple information requests (IRs).

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant indicated that the clinical trials were conducted in accordance with good clinical practice. The submission integrity was acceptable.

Four Bioresearch Monitoring (BIMO) inspection assignments were issued for this BLA. Three of the inspections were completed and classified as No Action Indicated (NAI). One inspection was cancelled due to COVID-19.
No significant inspectional findings were observed. Please refer to the BIMO memo for further details.

Table 3: BIMO Inspection Sites

Site ID	**Establishment for Inspection**	**FDA Form 483 Issued?**	**Inspection Status**
0002	MD Anderson Cancer Center Houston, Texas 77030	Cancelled	
0005	Massachusetts General Hospital Boston, Massachusetts 02114	No	No Action Indicated (NAI)
0007	City of Hope Duarte, California 91010	No	No Action Indicated (NAI)
0020	University of Colorado Cancer Center Aurora, Colorado 80045	No	No Action Indicated (NAI)

3.3 Financial Disclosures

A list of the 18 investigators were submitted. Complete financial disclosures were provided for the studies and reviewed. No significant financial interests or conflicts were identified that could potentially bias the conduct of the study. A complete list of clinical investigators was provided, and five investigators had disclosable financial interests/arrangements and submitted Form FDA 3455. These investigators had honoraria for conducting multiple clinical studies. Two investigators had a proprietary interest in JCAR017 and have not made a licensing agreement for potential royalty income. The details of the disclosable arrangements were provided along with a description of the steps taken to minimize potential bias. The investigators did not perform assessments for the 17001 study.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Lisocabtagene maraleucel (JACR017) is a CD19 directed genetically modified autologous T cell immunotherapy product that consists of CD4 and CD8 T cell components that are infused separately but sequentially (minutes apart). To prepare JCAR017, a subject's own T cells are harvested (via standard leukapheresis) and the purified CD4+ and CD8+ T cells are separately activated and transduced ex-vivo with a replication incompetent vector to express a chimeric antigen receptor (CAR) comprising an anti-CD19 FMC63 monoclonal antibody-derived single chain variable fragment (scFv), immunoglobulin (IgG) 4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain and a CD3 zeta activation domain. CD3 zeta signaling is critical for initiating T-cell activation and anti-tumor activity, while 4-1BB (CD13&) signaling is responsible for enhanced expansion and persistence of JCAR017. The transduced T cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved separately. The

JCAR017 formulation contains 75% volume by volume (v/v) Cryostor™ CS10 which contains 7.5% dimethylsulfoxide (v/v), 25% (v/v) multiple electrolytes for injection and 1% (v/v) of 25% human albumin. The product must pass a sterility test before release for shipping as a frozen suspension in subject -specific vials. The product is then thawed and infused back into the subject where anti-CD19 viable CAR-T cells can recognize and eliminate CD19 antigen positive tumor cells.

4.2 Assay Validation

Per Chemistry, Manufacturing and Controls (CMC) reviewer, the assays that were utilized for the JCAR017 manufacturing and cell persistence determination, and immunogenicity were validated.

4.3 Nonclinical Pharmacology/Toxicology

Per FDA's pharmacology and toxicology reviewer, no carcinogenicity or genotoxicity studies have been conducted with JCAR017.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology Review Memo for details.

4.4.1 Mechanism of Action

JCAR017 is prepared from the subject's T cells which are purified from the product of a standard leukapheresis procedure. The purified CD4+ and CD8+ T cells are separately activated and transduced with the replication incompetent lentiviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in culture and cryopreserved.

4.4.2 Human Pharmacodynamics (PD)

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.

4.4.3 Human Pharmacokinetics (PK)

JCAR017 cellular kinetics contains 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.

4.5 Statistical

Please see the statistical review memo for details.
The statistical reviewer verified the key endpoint analyses reported by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

The safety concerns of CRS and NT require that lisocabtagene maraleucel be available in the context of a REMS program with elements to assure safe use (ETASU) in place to ensure that benefits of receiving the drug product outweigh the risks. The following are the elements of the risk mitigation strategy:

FOR HOSPITALS

To become certified to dispense BREYANZI

- Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).
- Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program requirements on behalf of the hospital and associated clinic(s).
- Have the authorized representative complete the Live Training Program provided by the REMS Program
- Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program.
- Have the authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form and submitting it to the REMS Program.
- Train all relevant staff involved in prescribing, dispensing, or administering of BREYANZI on the REMS Program requirements using the Live Training Program.
- Have all relevant staff involved in prescribing, dispensing, or administering of BREYANZI successfully complete the Knowledge Assessment.
- Establish processes and procedures to ensure relevant new staff involved in the prescribing, dispensing, or administration of BREYANZI are trained and complete the Knowledge Assessment.
- Establish processes and procedures to verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours)
- Establish processes and procedures to provide patients with the Patient Wallet Card

Prior to infusion

- Provide the patient with the Patient Wallet Card
- Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program.

To maintain certification to dispense

- Have a new Authorized Representative enroll in the REMS Program by completing the Hospital Enrollment Form

To maintain certification to dispense, if BREYANZI has not been dispensed at least once annually from the date of certification in the REMS Program

- Train all relevant staff involved in prescribing, dispensing, or administering of BREYANZI on the REMS Program requirements using the Live Training Program.
- Have all relevant staff involved in prescribing, dispensing, or administering of BREYANZI successfully complete the Knowledge Assessment

At all times

- Report any serious adverse event suggestive of CRS or NT to the REMS Program
- Maintain records of staff training
- Maintain records that processes and procedures are in place and are being followed
- Comply with audits carried out by Juno Therapeutics Inc., or a third party acting on behalf of Juno Therapeutics, Inc., to ensure that all training, processes, and procedures are in place and are being followed

FOR APPLICANT:
The Applicant must provide training to relevant staff who prescribe, dispense or administer BREYANZI. Training includes: i) Live Training Program ii) Knowledge Assessment. The training must be provided in-person or via live webcast.

To support REMS program operations, Applicant (JUNO Therapeutics Inc.) must ensure the following:

- Ensure BREYANZI is distributed only to certified hospitals or their associated clinics.
- Establish and maintain the REMS Program website, www.BreyanziREMS.com. The REMS Program website must include the option to print the Prescribing Information (PI), Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS program website must not link back to the promotional product website(s).
- Make the REMS Program website fully operational and all REMS materials available through website and call center.
- Establish and maintain a REMS Program Call Center for REMS participants at 1-888-423-5436.
- Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
- Ensure hospitals and their associated clinics are able to enroll in the REMS Program in person, online, fax and telephone.
- Notify hospitals and their associated clinics within 7 calendar days after they become certified in the REMS Program

To ensure REMS participants' compliance with the REMS program, Juno Therapeutics, Inc. must:

- Verify annually that the designated authorized representative for certified hospitals and their associated clinics remains the same. If different, the hospital and their associated clinics must re-certify with a new authorized representative.
- Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: BREYANZI distribution and dispensing; certification of hospitals and their associated clinics, and audits of REMS participants. These records must be readily available for FDA inspections.
- Monitor hospitals and their associated clinics on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
- Maintain an ongoing annual audit plan of hospitals and their associated clinics.
- Audit all certified hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of BREYANZI to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Certified hospitals and their associated clinics must also be included in Juno Therapeutics, Inc.'s, ongoing annual audit plan.
- Take reasonable steps to improve implementation of and compliance with the requirements in the BREYANZI REMS Program based on monitoring and evaluation of the BREYANZI REMS Program.

The pharmacovigilance plan includes a long-term, observational registry study for patients treated with JCAR017. This PMR study will follow the recipients of JCAT017 for 15 years to characterize the incidence and severity of selected AEs, including secondary malignancy. Secondary malignancies must be reported by treating physicians to the Applicant within 72 hours of diagnosis to expedite AE reporting and to initiate a separate, non-protocol-related process for tumor specimen processing, and testing for JCAR017 vector sequence for secondary malignancies of T cell origin.

Clinical reviewer comments

The safety review was based on 268 subjects with the original data cutoff of April 12, 2019. The efficacy reviewer chose to evaluate data with a later cutoff date of August 12, 2019 wherein 1 more subject was enrolled and there was longer follow up data. The safety reviewer did not choose the 4-month update data cutoff like the efficacy reviewer since safety events were adequately captured at the time of the original data cutoff of April 12, 2019.

The REMS with ETASU and the PMR safety study are the recommendation of the clinical review team with concurrence from the pharmacovigilance reviewers from the Center for Biologics Evaluation and Research (CBER) Office of Biostatistics and Epidemiology (OBE), Center for Drug Evaluation and Research (CDER) Division of Risk Management (DRISK), and the CBER Safety Working Group. The goal of the REMS is to ensure that sites are prepared for the safety risks of JCAR017 that were identified in the IND phase of product development. The PMR registry study addresses the theoretical concerns of insertional mutagenesis and/or the development of a JCAR017 related secondary malignancy. The applicant is proposing to enroll approximately 1500 patients (500 from clinical trials) and follow each patient for up to 15 years.

The clinical review team recommends that the label inform of the requirement to monitor patients at the certified healthcare facility daily for at least seven days following infusion of JCAR017 for signs and symptoms of CRS and neurologic events. This recommendation is based on the requirements in the protocol, the clinical data related to the timing of onset of neurologic and CRS events, and the availability of guidance to treat these serious adverse events. The knowledge of and experience with CAR-T cell therapy products has expanded over the intervening years, and with adequate safety procedures in place, outpatient monitoring is considered acceptable after lisocabtagene maraleucel infusion.

Discussions with the applicant are ongoing regarding the final REMS and ETASU documents. Please refer to the action letter for final wording of the PMR.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The review of the clinical efficacy was based upon Study 17001 clinical study report, case report forms, and submitted data, in addition to multiple information requests. Primary efficacy analyses were verified and exploratory analyses were conducted using JMP 15 software.

The clinical review was primarily based upon Study 17001 with the efficacy data cut off of 12/18/2019 for 269 subjects. The protocol design is described in section 6.1.2 Design overview.

A major amendment regarding a substantial amount of new manufacturing and facility information which was not previously submitted or reviewed added an additional three months to the review clock.

The clinical safety review was primarily based upon analysis of 268 subjects in the DLBCL cohort in study 017001 at the primary data cutoff date of 12 April 2019. There is a difference of 1 subject between the safety and efficacy reviews given that safety was analyzed at the original data cutoff of April 12, 2019 and efficacy was analyzed using the 4-month data update with a longer follow up. Given that safety was adequately captured at the original data cutoff, it was decided not to use the 4-month updated data cutoff of August 12, 2019 for safety analysis. This discrepancy has been explained in the label as well. The study 017001 protocol design is described in 6.1.2 Design Overview. Dose level plus dose schedule constituted a dose regimen in study 017001. Subjects assigned to all dose regimens were studied-single dose level 1 (DL1S), single dose level 2 (DL2S), single dose level 3 (DL3S), two dose level 1 (DL1D) and two dose level 2 (DL2D). Only 6 of 268 large B-cell lymphoma subjects were included in the latter 2 dose (DL1D, DL2D) regimens. Review of safety included review of the following: clinical study report (CSR), summary of clinical safety (SCS), ISS, analysis of datasets relevant to safety for study 017001, subject narratives, case report forms (CRFs) if needed, information in numerous information requests (IRs) and data in the public domain. JMP 14 was used to reproduce key safety analyses based on submitted analysis (ADaM) datasets.

Supportive data from studies BCM-001. BCM-002 and 017007 were included in the 3rd line or later therapy setting of large B-cell lymphoma (see 5.3 Table of Studies/Clinical Trials

for details of these studies) were provided by the Applicant in the integrated summary of safety (ISS) datasets. However, study 017007 had no subjects who were treated and the safety data from studies BCM-001 and BCM-002 were deemed to be not different from that of study 017001 and given the small number of subjects in these studies and the adequate sample size of 268 subjects in the large B-cell lymphoma population in study 017001, a decision was made not to include these additional studies for detailed safety analyses or in the safety information in the label. Additional studies reported by the Applicant in the ISS but not in the 3rd line or later therapy setting or for diagnosis other than large B-cell lymphoma were not included in the safety analyses given differences in study population and adequacy of the primary study for safety analysis.
The 120-day safety update with a data cutoff date of 12 August 2019 had one additional subject in the large B-cell lymphoma cohort in study 017001; no new safety signals were identified. Findings in the safety update review are provided at the end of 6.1.12.6 Clinical Test Results.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review
Please see 5.1 Review Strategy.

5.3 Table of Studies/Clinical Trials

Study 017001 is the study on which safety and efficacy analyses of this BLA application is based. Two hundred and sixty-eight subjects who received JCAR017 are included in the analyses of safety with the primary data cutoff date as in Table 4. The efficacy analysis includes 256 subjects with an updated data cutoff that is 4 months later than the primary data cutoff. Two other studies outlined in Table 5 in 3rd line or later (3L+) relapsed/refractory DLBCL were included in the integrated safety summary (ISS). A fourth study, 017007, also in the 3rd line DLBCL setting did not enroll any subjects as of original data cutoff. Four other studies (Table 6) were included in the Applicant's narrative of the ISS but these are studies not in the 3rd line or later relapsed/refractory DLBCL setting.

Table 4. Overview of primary study of JCAR017 after lymphodepletion

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
017001	Single arm, open-label, multicenter Phase 1 study Dose Cohorts: DL1S: 50 x 10^6 DL2S: 100 x 10^6 DL3S: 150 x 10^6 DL1D: 50 x 10^6, two-dose DL2D: 100 x 10^6, two-dose	Age ≥ 18 years with relapsed/ refractory large B-cell lymphoma	ORR per IRC	DLBCL N=268 for safety N=269 for efficacy	April 12, 2019 for safety August 12, 2019 for efficacy

Source: FDA analysis
Abbreviations: DL1S: dose level 1 single, DL2S: dose level 2 single, DL3S: dose level 3 single, DL1D: dose level 1 two-dose, DL2D: dose level 2 two-dose, ORR: objective response rate, IRC: independent review committee, DLBCL: diffuse large B-cell lymphoma

Clinical Reviewer Comments

- *Two hundred and sixty-eight subjects with large B-cell lymphoma received conforming product in the DLBCL cohort and were considered the safety analysis population. An additional 24 subjects although treated, received non- conforming product.*
- *There was a two-dose schedule in dose level 1 and 2-termed DL1D, DL2D respectively. These subjects received another dose of JCA017 ~14 days following the 1st JCAR017 dose; lymphodepletion was not repeated. Very few subjects were in these two dose schedules*
- *Diffuse large B cell lymphoma (DLBCL) cohort included subjects with DLBCL not otherwise specified (NOS) and transformed from indolent Non-Hodgkin lymphoma (NHL), double and triple hit lymphomas (MYC with and without BCL2 and/or BCL6), primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma (FL) grade 3B*
- *Mantle cell lymphoma cohort is also included in the 017001 study, but is not the focus of this BLA*

Table 5. Overview of supportive studies providing additional safety data in 3rd line or later therapy setting

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
BCM-001	Single arm, open-label, multicenter, multicohort Phase 2 study Dose: 100 x 10^6 cells	Age ≥ 18 years with R/ R aggressive B-cell NHL	ORR	DLBCL* N=20	February 22, 2019
BCM-002	Phase 1/2, open-label, multi-arm, parallel, multicohort, multicenter study of JCAR017 in combination with Durvalumab (Arm A) or CC-122 (Arm B)** Dose of JCAR017 Arm A: DL1: 50 x 10^6 cells DL2: 100 x 10^6 cells Arm B: 100 x 10^6 cells	Age ≥ 18 years with R/R aggressive B-cell NHL after 2 or more lines of systemic therapy	Safety for Phase 1 CR at 3 and then 6 months for Phase 2	23 (16 from Arm A and 7 from Arm B)	February 22, 2019
017001 (TRANSCEND OUTREACH)	Single-arm, open-label, multicenter, Phase 2 study of JCAR017 in the outpatient setting	Age ≥ 18 years with R/R large B-cell NHL after 2 or more lines of	Safety	None	February 22, 2019

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
	(non-tertiary care setting)	systemic therapy			

**Data from cohort 1 (Europe) and 3 (Japan) which mirrors population in study 017001*
*** Data from BCM-002 trial collected before addition of Durvalumab or CC-122*
Abbreviations used: R/R: relapsed/refractory, ORR: overall response rate, CR: complete response, DL1: dose level 1; DL2: dose level 2, NHL: non-Hodgkin lymphoma

Clinical reviewer comments

- *We reviewed only study 017001 in detail for safety since we felt that 268 subjects with large B-cell lymphoma were adequate for a safety analysis and the addition of 43 subjects from study BCM-001 and BCM-002 would not add much to the safety analyses*
- *We did a topline review of the safety dataset (ADAE dataset) for studies BCM-001 and BCM-002 and did not identify any new safety signals*

Table 6. Other Studies of JCAR017

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
017004	Open-label, multicenter Phase 2 study of JCAR017 monotherapy and combination therapy with Ibrutinib Dose Cohorts: DL1: 50 x 10^6 cells DL2: 100 x 10^6 cells	Age ≥ 18 years with R/R CLL/SLL	Phase 1 Safety Phase 2 CRR	23	February 22, 2019
017006	Open-label, single arm, multicenter Phase 2 trial Dose: 100 x 10^6 cells	Age ≥ 18 years with R/R CD19+ NHL with 1 or more prior line of therapy and TNE	ORR	5	February 22, 2019

Trial	Design	Population	Primary Endpoint	N Treated	Data Cutoff
BCM-004	Phase 1/2, open-label, single-arm, multicohort, multicenter, 2-stage study	Age < 18 years (phase 1); , 25 years of age (phase 2) Phase 1: R/R B-ALL Phase 2: Cohort 1: R/R B-ALL Cohort 2: MRD+ B-ALL Cohort 3: R/R B-NHL with one or more prior line of therapy	Phase 1: RP2D Phase 2: ORR	1	February 22, 2019

Abbreviations used: CLL: chronic lymphocytic leukemia, SLL: small lymphocytic lymphoma, NHL: Non-Hodgkin lymphoma, CRR: Complete Response Rate, ORR: overall response rate, R/R-relapsed/refractory, ALL: acute lymphoblastic leukemia, MRD: minimal residual disease,DL1: dose level 1; DL2: dose level 2; RP2D: recommended phase 2 dose, TNE: transplant non-eligible

Clinical reviewer comment

Table 6 represents studies in either diagnoses other than large B-cell lymphoma or in settings other than 3rd line treatment.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

The application was not presented to an Advisory Committee as it did not raise significant efficacy concerns or any new safety concerns.

5.4.2 External Consults/Collaborations

The application was not presented to external consultants or collaborators.

5.5 Literature Reviewed (if applicable)

1. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol*. 2016;174(1):43-56.
2. Farooq U, Maurer MJ, Thompson CA, et al. Clinical heterogeneity of diffuse large B cell lymphoma following failure of front-line immunochemotherapy. *Br J Haematol*. 2017;179(1):50-60.
3. Zelenetz AD, Gordon GI, Abramson JS, Advani R, Bartlett NL, Caimi PL. NCCN Guidelines: B-Cell Lymphomas, Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed 11 May 2020.
4. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190.
5. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.
6. Hitz F, Connors JM, Gascoyne RD, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. *Ann Hematol*. 2015;94(11):1839-1843.

7. Nagle SJ, Woo K, Schuster SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *Am J Hematol*. 2013;88(10):890-894.
8. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant*. 2016;51(1):51-57.
9. Lee DW, Santomasso BD, Locke FL, et.al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant.* 2019; 25 (4): 625-638.
10. Santomasso BD, Bachier C, Westin J, et. al. The Other Side of CAR-T Cell Therapy: Cytokine Release Syndrome, Neurologic Toxicity, and Financial Burden. *American Society of Clinical Oncology Education Book*. 2019; Book 39: 433-444.
11. Lee DW, Gardner R, Porter DL, et. al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014; 124 (2): 188-195.
12. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al.
Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

6.1 Study 017001 (TRANSCEND)

Study 017001 was the pivotal study that constitutes the primary evidence of safety and efficacy of JCAR017 in the treatment of adult subjects with R/R B-cell NHL after at least two prior therapies.

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to evaluate the safety of JCAR017 in adult subjects with R/R B cell NHL and to assess the antitumor activity where the overall response rate is the primary endpoint., as determined by an Independent Review Committee applying the 2014 Lugano criteria.

Secondary objectives included:
1) to assess the rate of compete response (CR) and durability of antitumor activity where duration of response (DOR) was defined as time from first response to progressive disease (PD) or death.
2) to estimate the PFS and OS of subjects where PFS was defined as the time from first infusion to PD or death
3) to characterize the PK profile
4) to assess HRQoL and health economics and outcomes research
Exploratory objectives included:

1) to assess effect of antitumor activity using Bayesian methods
2) to assess immune responses
3) to assess pharmacodynamics effects
4) to assess the effect of JCAR017 attributes on safety, PK and antitumor activity
5) to assess the effect on tumor and antitumor environment

6.1.2 Design Overview

Study 017001 was an open-label, multicenter, multicohort, Phase 1 study to determine the safety, antitumor activity, and PK of JCAR017 in adult subjects with R/R DLBCL not otherwise specified (NOS; de novo and transformed from indolent lymphoma), 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 MCL.

Reviewer Comment: The DLBCL cohort was the focus of the BLA application as the applicant did not seek an indication in subjects with MCL.

6.1.3 Population

Key Inclusion criteria included:
-Age over 18 years old
-Relapsed or refractory B cell NHL of the following histologies:
DLBCL Cohort: DLBCL, not otherwise specified (NOS; includes transformed
DLBCL from indolent histology [transformed iNHL]), HGL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, and FL3B. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have R/R disease after at least 2 lines of therapy or after autologous hematopoietic stem cell transplant (auto-HSCT).
b. MCL Cohort: MCL (diagnosis must be confirmed with cyclin D1 expression or
evidence of t(11;14) by cytogenetics, fluorescence in situ hybridization [FISH], or polymerase chain reaction [PCR]) with relapsed or refractory disease after at least
1 prior line of MCL therapy
-PET positive disease per Lugano criteria
-ECOG performance status of 0 or 1
-Adequate organ function
-Subjects with prior CD19 therapy with CD19 positive lymphoma confirmed on biopsy

Key Exclusion criteria included:
-Subjects with central nervous system (CNS) only involvement by malignancy (subjects with secondary CNS malignancy were allowed on study)
-History of another primary malignancy that had not been in remission for at least 2 years
-Treatment with alemtuzumab within 6 months of leukapheresis
-Treatment with fludarabine or cladribine within 3 months of leukapheresis
-Active Hepatitis B, C or HIV at time of screening
- Subjects with uncontrolled infection at the time of leukapheresis or JCAR017 administration
-Presence of acute GVHD
-History or presence of clinically relevant CNS pathology
-Immunosuppressive therapy within four weeks of leukapheresis and JCAR017 administration
-Donor Lymphocyte Infusion within 6 weeks of study drug administration
-Radiation within 6 weeks of leukapheresis
-Allogeneic stem cell transplant within 90 days of leukapheresis

6.1.4 Study Treatments or Agents Mandated by the Protocol

Leukapheresis: Following screening, leukapheresis was performed on each subject to collect a sufficient quantity of peripheral blood mononuclear cells to produce the product.

Bridging Therapy: Per the treating physician, bridging therapy was allowed for disease control during the manufacturing process. Prior to study drug treatment, PET/CT scans were performed following bridging therapy. The following were not included as bridging therapy and therefore PET/CT was not required following administration of the following treatments:
-Prednisone ≤ 20mg/day (7 subjects)
-Radiation therapy to a single lesion for symptom management (2 subjects)
-Intrathecal chemotherapy alone (one subject)

Reviewer Comment:
PET positive disease based on IRC assessment was required for eligibility post bridging therapy. These subjects are the JCAR017 treated Efficacy Analysis Set. Subjects who did not have a baseline PET/CT assessment repeated after bridging therapy for disease control and before JCAR017 administration were excluded from the Efficacy Analysis set. Among those who were eligible for JCAR 017 (n=256), 150 subjects (59%) received the bridging therapy. Therapies that were given in ≥10% of the subjects included:

- *Rituximab 88 subjects (34.4%)*
- *Gemcitabine 53 subjects (20.7%)*
- *Dexamethasone 39 subjects (15.2%)*
- *Oxaliplatin 39 subjects (15.2%)*
- *Cyclophosphamide 27subjects (10.5%)*
- *Corticosteroids (including dexamethasone, prednisone, methylprednisolone, hydrocortisone) 70 subjects (27%)*

Ten subjects received bridging therapy that was considered exempt from needing a repeat PET/CT after completion. These are reasonable exemptions and in a small subset of the efficacy evaluable population.

Lymphodepleting Conditioning Chemotherapy: Subjects were treated with lymphodepleting chemotherapy (Fludarabine 30mg/m2/day and cyclophosphamide 300mg/m^2/day for 3 days) between 2 and 7 days prior to JCAR017 administration.

JCAR017: Premedication with acetaminophen and diphenhydramine were given 30-60 minutes prior to administration and could be repeated every 6 hours per the investigator's assessment. Premedication with steroids was not allowed. Subjects were administered according to the dose regimen to which a subject was assigned, which is described below.

- **Dose Level 1:** 50 x10^6 CAR+ T cells
- **Dose Level 2:** 100 x10^6 CAR+ T cells
- **Dose Level 3:** 150 x10^6 CAR+ T cells

For subjects who received two doses of JCAR017 (Dose level 1 only), this was given on Day 1 and on D15. Lymphodepletion was not given prior to the second dose of JCAR017. Additional cycles or retreatment cycles were initially allowed in the protocol and subsequently removed.

Lymphodepleting chemotherapy was to be completed between 2 and 7 days before JCAR017 administration.

Reviewer Comment:
If subjects received an additional cycle, the efficacy endpoint of best overall response was analyzed after the first infusion. If subjects were retreated, the efficacy endpoint of best overall response was analyzed prior to the retreatment cycle. This analysis ensures that these subjects could be part of the efficacy analysis set. Seven subjects had additional cycles and 16 subjects were retreated.
The preliminary evidence for efficacy supported by the applicant was a target dose of 100 x10^6 CAR+ T cells.

6.1.5 Directions for Use

JCAR017 was supplied cryopreserved in subject specific vials and thawed prior to administration. The product was infused intravenously. Instruction regarding storage and administration are detailed in the approved label.

6.1.6 Sites and Centers

Fourteen sites in the USA participated in the trial. Of the 14 sites, 64.3% prepared the dose in a cell therapy lab, 28.6% of sites prepared the dose at the bedside, and 7.1% of sites thawed at a cell therapy lab and prepared the dose at bedside.

6.1.7 Surveillance/Monitoring

The applicant ensured appropriate monitoring procedures were performed before during and after the study.
The following is the schedule of events during the study including monitoring throughout the study and post treatment.
Figure 1: Monitoring Procedures

	Pre-Treatment[a]		Treatment															Posttreatment (Follow-Up[c], EOS)						
			Two-Dose Schedule[b]																					
			Single-Dose Schedule																					
	Screening	Evaluation	JCAR017 Dose #1								JCAR017 Dose #2													
Study Day	-28		-4 to -2[a,d,n]	1[d]	4	8	11	15[e]	22[e]	29[e]	1[d,e]	4	8	11	15	22	29	60	90	180[ff]	270[ff]	365	545	730
Visit Window					±1	± 1	± 1	± 2	± 2	± 2		±1	± 1	± 1	± 2	± 2	± 2	± 14	± 14	-14, + 28	- 28, + 14	± 14	± 14	± 14
Procedure																								
Obtain consent	x																							
I/E criteria	x	See Prot Sec 6.2[v]																						
Medical history	x																							
12-lead ECG		x[bb]																						
MUGA/ECHO	x																							
Viral serology	x																							
Serum pregnancy	x	x[v]																						
HLA typing		x[f]																						
Donor chimerism		x[g]																						
Archived tumor biopsy		x																						
Leukapheresis		x[h]																						
Lymphodepleting chemo			x[i]																					
JCAR017 administration				x							x													
AEs/SAEs	AEs/SAEs related to protocol-mandated procedures		Collect all AEs/SAEs from LDC to 90 days after the last dose of liso-cel[s,ee, ff]																	AEs/SAEs related to liso-cel and/or protocol-mandated procedures[j,s]						
Concomitant Medications	Con meds associated with AEs/SAEs related to protocol-mandated procedures		Collect all concomitant meds from LDC to 30 days after the last dose of investigational product (either LDC or JCAR017)															Concomitant meds ongoing at the time of AEs/SAEs related to liso-cel and/or protocol-mandated procedures						
Anticancer Therapies			Throughout study																					
Hospitalizations			From first day of LDC to end of study																					
Height/Weight		x[v]		x[k]																				
Physical examination	x	x[v]		x		x		x	x	x	x		x		x	x	x	x[l]	x[l]	x[l]	x[l]	x		x
Vital signs		x[v]	x	x[t]	x	x	x	x	x	x	x[t]	x	x	x	x	x	x							
ECOG	x	x[v]	x	x		x		x	x	x	x		x		x	x	x							
Formal neuropsych		x																	x[l]	x[l,w]				
Routine neuro	x	x[v]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x[l]					
MMSE		x[v]		x	x	x		x		x	x	x	x		x		x		x[l]					
PET and CT	x[m]	x[bb,cc]								x[n]							x[n]		x[o]	x[o]	x[o]	x[o]	x[o]	x[o]
Chemistries/Hematology	x	x[v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x							

	Pre-Treatment[a]		Treatment														Posttreatment (Follow-Up[c], EOS)						
			Two-Dose Schedule[b]																				
			Single-Dose Schedule																				
	Screening	Evaluation	JCAR017 Dose #1								JCAR017 Dose #2												
Study Day	-28		-4 to -2[a,d,n]	1[d]	4	8	11	15[e]	22[e]	29[e]	1[d,e]	4	8	11	15	22	29	60	90	180[ff]	270[ff]	365	545	730
Visit Window					±1	± 1	± 1	± 2	± 2	± 2		±1	± 1	± 1	± 2	± 2	± 2	± 14	± 14	-14, + 28	- 28, + 14	± 14	± 14	± 14
Procedure																								
Coagulation		x[v]		x	x	x	x	x	x	x	x	x	x	x	x	x	x							
Inflamm. Markers		x[v]		x	x	x	x	x	x[p]	x[p]	x	x	x	x	x	x[p]	x[p]							
Immunoglobulins		x[v]						x	x	x					x	x	x	x[aa]	x[aa]	x[aa]	x[aa]	x[aa]	x[aa]	x[aa]
Fresh tumor biopsy		x[bb,dd,r]					x[q,r]																	
Immunogenicity		x						x		x	x				x		x	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]
PK by flow cytometry		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Viral vector sequence by qPCR		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[z]	x[z]	x[z]
Biomarkers		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]
RCL testing		x																	x	x		x		x[y]
HRQoL		x		x						x	x						x	x	x	x	x	x	x	x

Source Original BLA 125714/0 Report Body 9.5.1 Table 3 Page 51-52 of 290

An independent Data Safety Monitoring Board (DSMB) reviewed cumulative study data from Study 017001 approximately every 3 months over the course of the study to evaluate safety, protocol conduct, and the scientific validity and integrity of the trials. Ad hoc meetings of the DSMB were held if safety events occurred which either the DSMB and/or the sponsor felt required urgent evaluation by the DSMB members.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoints included:
-Type, frequency, and severity of AEs and laboratory abnormalities
-p[DLT] estimated by the modified continual reassessment method (mCRM)
-ORR (CR + PR)

Reviewer Comment:
The primary endpoint of ORR was defined as the proportion of subjects with a BOR of either CR or PR and was assessed as per the IRC-FDA algorithm which was agreed upon at the pre-BLA meeting referenced above. All subjects who did not meet the criteria for an objective response by the analysis cut-off were considered as non-responders. The efficacy objectives were added later as the study transitioned from a dose escalation study to a primary study intended for marketing applications and therefore evaluation of the safety endpoints were included in the primary objective.

Secondary endpoints included:
-CR rate
-DOR, defined as the time from first response to PD or death
-PFS, defined as the time from first infusion to PD or death; PFS ratio
-OS, defined as the time from treatment with JCAR017 to the date of death
-PK parameters
-Quality of life and outcomes research

The secondary endpoints included:
-CR rate, defined as the proportion of subjects with a BOR of CR by IRC assessment based on the Lugano 2014 criteria
-DOR, defined as the time from first response (CR or PR) to PD or death by IRC assessment based on the Lugano 2014 criteria
-PFS, defined as the time from first infusion of JCAR017 to PD or death by IRC assessment based on the Lugano 2014 criteria
- PFS ratio, defined as the ratio of PFS on the most recent line of therapy prior to

JCAR017 to the PFS on JCAR017
-OS, defined as the time from treatment with JCAR017 to the date of death
-Measurement of HRQoL changes as assessed using the EORTC QLQ-C30 and the (b) (4)
-Numbers of ICU inpatient days and non-ICU inpatient days and reasons for hospitalizations.

6.1.9 Statistical Considerations & Statistical Analysis Plan

For safety, treatment-emergent adverse events were defined as any adverse event with onset during or after study drug infusion; to be summarized by preferred term and toxicity grade. Adverse events of special interest (AESI): Previously identified risks of study treatment—cytokine release syndrome (CRS), neurologic events, cytopenias, infections, and hypogammaglobulinemia.

For efficacy, the study tested the hypothesis for the primary efficacy endpoint that ORR > 40% against the null hypothesis that the ORR ≤ 40% at a 1-sided 1% and 2.1% level of significance at the interim and primary analysis, respectively, powered for ORR = 65%, ie, H0: ORR ≤ 40% versus H1: ORR > 40%

The ORR is calculated along with the 2-sided 95% exact Clopper-Pearson confidence intervals (CIs).

The study tested the hypothesis that the CR rate > 20% against the null hypothesis that the CR rate ≤ 20% at a 1-sided 1% and 2.1% level of significance at the interim and primary analysis, respectively, powered for CR rate = 40%, ie, H0: CR rate ≤ 20% versus H1: CR rate > 20%
The ORR was defined as the proportion of subjects with a BOR of either CR or PR. The BOR was the best disease response recorded from the time of the final JCAR017 infusion of the initial cycle until disease progression, end of study, the start of another anticancer therapy, or HSCT. Best response was assigned according to the following order: CR, PR, SD, PD, not evaluable, or not done. In the IRC analysis, a non-PD was
assigned as a BOR by the IRC when PET was not evaluable or not done for all the post-baseline assessment time points and the best response based on CT-staging evaluation was CR, PR or SD.

Duration of response was evaluated based on the IRC evaluations for subjects who achieved a CR or PR based on the Lugano 2014 criteria. The date of first response and the date of progression was assigned by the IRC. In the case that a subject did not have disease progression or death prior to the data cutoff date, DOR was censored at the date of the last adequate disease assessment on or prior to the earliest censoring event.

Key Censoring rules included:
For assessment of DOR, PFS and OS, loss to follow-up subjects would be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event. Data from surviving subjects were censored at the last time that the subject was known to be alive.

Reviewer Comment:
Please refer to Statistical review for detailed information.

6.1.10 Study Population and Disposition

All subjects who received JCAR017 were evaluated for safety. All of these subjects had been leukapheresed. Subjects who received nonconforming product were not evaluated. The JCAR017-treated Efficacy Analysis Set included all subjects in the DLBCL Cohort and JCAR017-treated Analysis Set who had PET-positive disease present before JCAR017 administration based on IRC assessment. Subjects who did not have baseline PET/CT assessment repeated after bridging therapy for disease control and before JCAR017 administration were excluded from the JCAR017-treated Efficacy Analysis Set.

6.1.10.1 Populations Enrolled/Analyzed

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 having received at least 1 prior line of therapy
(A total of 17 subjects were treated in the MCL cohort)

For the DLBCL cohort, the summary prior systemic therapy is as below.

Table 7: Summary of Prior Systemic Therapy

Prior Regimen (systemic therapy)	N=268
1	9
2	121
3	68
4	43
≥5	27

Reviewer Comment:
The safety and efficacy review will only entail subjects in the DLBCL cohort as the applicant is seeking this indication and will be part of the final label. The nine subjects who received one prior line of systemic therapy, but a total of 2 prior lines of therapy were allowed on study.

All subjects who were treated with JCAR017 with the conforming product were evaluated for safety.
As stated above, subjects must have had PET positive disease present before JCAR017 administration based on IRC assessments. Subjects who did not have baseline PET/CT assessment repeated after bridging therapy for disease control and before JCAR017 administration were excluded. This set was used for the primary efficacy analysis.

Reviewer Comment:
The efficacy discussion will only include subjects in the primary efficacy analysis.

The dose levels (DLs) allowed in this study were:
DL1: 50×10^6 CAR+ T cells
DL2: 100×10^6 CAR+ T cells
DL3: 150×10^6 CAR+ T cells

Dose selection for each subject occurred after leukapheresis and was dependent on the dosing groups open at the time of assignment.

6.1.10.1.1 Demographics

Table 8: Demographics of Treated Population

	N (%)
All	268 (100%)
Age Category	
< 65 Years	157 (59%)
>/= 65 Years	111 (41%)
>/= 75 Years	27 (10%)
Sex	
Female	94 (35%)
Male	174 (65%)
Race	
Black or African American	12 (4.5%)
Asian	11 (4.1%)
White	231 (86.2%)
Multiple	1 (0.4%)
American Indian	2 (0.7%)
Not reported	11 (4.1%)
Ethnicity	
Hispanic or Latino	26 (10%)
Not Hispanic or Latino	232 (87%)
Unknown	10 (4%)

Reviewer Comment:
The demographic characteristics are displayed for the DLBCL treated/safety analysis set. The study population appears representative of those with DLBCL. The median age was 63 years with a predominance of males and whites.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Half of the DLBCL treated subjects had DLBCL NOS (137 of 268 [51.1%]) followed by DLBCL transformed from FL (60 of 268 [22.4%]), HGL including DLBCL with double/triple hit (36 of 268 [13.4%]), PMBCL (15 of 268 [5.6%]), and FL3B (2 of 268 [0.7%]). Additionally, 7 of 268 subjects (2.6%) had CNS involvement of lymphoma at the time of JCAR017 infusion (Refer to 6.1.11.3) . Out of the 268 subjects, 212 (79.1%) were refractory and 56 (20.9%) were relapsed.

Eligibility criteria for enrollment allowed at least two lines of therapy and required prior receipt of an anthracycline and rituximab (or another CD20-targeted agent).

The median for prior systemic therapies was three lines. There were 94 subjects (35.1%; 90 autologous and 9 allogeneic) who underwent HSCT.

Reviewer Comment: Per the data cutoff of 8/2019, one additional subject is included in the efficacy evaluable population n=256. For the safety review, 268 subjects will be reviewed.

6.1.10.1.3 Subject Disposition
In the DLBCL trial, 347 subjects were screened. 344 were leukapheresed, and 269 received JCAR017. There were 75 subjects who were not treated due to manufacturing failures or due to death or disease complications.

Out of the 269 who received the product, the DLBCL efficacy evaluable set included 256 subjects.

Thirteen subjects from the DLBCL Treated Set were excluded from the DLBCL Efficacy Set for the following reasons:
Six subjects were excluded because they had bridging therapy for disease control but did not have a PET scan after that therapy and before JCAR017 infusion
Four subjects were excluded because they did not have PET-positive disease at baseline
Three subjects were treated with product manufactured using the original manufacturing process.

Manufacturing failure occurred in 39 of 341 (11.1%); 25 of these subjects received infusion of the nonconforming product. Twelve subjects did not receive the product due to the product not being able to be manufactured. Ten of the 12 subjects had a manufacturing failure and did not receive product due to death, ineligible to receive (did not have PET positive disease), withdrew consent, and one subject decided to pursue another treatment.

Reviewer Comment:
Three of the 344 subjects in DLBCL leukapheresed set were excluded from the denominator as one subject underwent leukapheresis but withdrew from the study before manufacture was initiated. Two other subjects withdrew from the study after manufacture was initiated but before release testing.

An attempt to re-manufacture from the first leukapheresis was made in one subject, by manufacturing from a second leukapheresis in 17 subjects, and by re-manufacturing from the second leukapheresis in zero subjects.

Out of the 18 subjects, a conforming product was obtained in 10 subjects.
Reviewer Comment:
Of the 18 subjects that were re-manufactured, seven subjects had a response.

The time from leukapheresis to JCAR017 infusion was a median of 37 days (range of 27-224 days). The median time from last dose of lymphodepleting chemotherapy to JCAR017 treatment was 4 days (range 3 to 9 days).

Reviewer Comment: Subjects did not always receive the study drug immediately upon availability at the investigator's discretion. These delays were due to AEs experienced by the subject. There were 192 subjects (56.1%) that had an AE from leukapheresis to lymphodepletion.

6.1.11 Efficacy Analyses

The efficacy analyses include all subjects in the DLBCL cohort who received at least one dose of JCAR017 and excluding subjects who received nonconforming product as their first dose.

As stated above, the leukapheresed set includes all leukapheresed subjects in the DLBCL cohort (344 subjects). Subjects could receive bridging therapy post leukaphereses. There were 150 subjects (59%) who received the bridging therapy. Six of these subjects who had bridging did not have a PET scan prior to JCAR017 infusion.

There were 269 subjects who received JCAR017.
The results are presented for the different assigned dose regimens. The leukapheresed set includes all leukapheresed subjects in the DLBCL cohort.

Reviewer Comment: As stated above there were 13 subjects who received JCAR017 who were excluded from the DLBCL efficacy analysis because they did not have PET positive disease post bridging or no PET was done. Three subjects did not get the conforming drug product and were not evaluated for efficacy.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis was based on ORR as assessed using the 2014 Lugano Classification. Baseline disease and disease response were assessed at each timepoint by the investigator and by an Independent Review Committee (IRC). An oncology review was performed for all efficacy evaluable subjects.
Based on agreements made during the pre-BLA meeting, the FDA IRC Algorithm assessment was used for all subjects.

The following assessments were made for BOR:
Table 9: BOR assessments

PET + Clinical Response	CT + Clinical Response	PET + CT +Clinical Overall Response
CMR	CR/PR/SD/NE/NonPD	CR
PMR	CR/PR/SD/NE/NonPD	PR
NMR	CR/PR/SD/NE/NonPD	SD
NE	CR/PR/SD/NE/NonPD	Non-PD
NE	NE	NE
Any	PD	PD
PMD	ANY	PD

In the IRC analysis, a non-PD could be assigned as a BOR by the IRC when PET was not evaluable or not done for all the postbaseline assessment time points and the best response based on CT-staging evaluation was CR,PR, or SD. In such a case, a subject was considered as a non-responder in the calculation of ORR.

Two central radiologists read each subject's images. If the central radiologists' assessments differed, a third radiologist acted as an adjudicator. After adjudication (if applicable), a central clinician reviewed the imaging data in conjunction with clinical data to provide a final central disease status assessment.

If there was discordance in any of the four following variables- Best Overall Response (BOR) from PET-staging, Date of Progression (DOP) from PET-staging, DOP from CT-staging, and Date of First Response (DOFR) from PET-staging, an adjudication was performed. The adjudicator reviewed, but did not re-read, the two primary reads. The adjudicator chose the read that he or she believed most accurately represented the adjudication variable. In the event that more than one of the four variables are discordant,

the adjudicator selects the read of the primary reader that aligns best with the adjudicator assessment based on agreement with the highest order variable.

Reviewer Comment: As PET and CT assessments sometimes do not necessarily align, an adjudication would not occur for discordance between PET BOR and CT BOR which is acceptable.

Per the study protocol, follow up by a PET scan was no longer required once CMR was achieved by the investigator's assessment. There were 74 subjects that were assigned a non-PD when a PET was not evaluable or not done. Three of these subjects were not part of the DLBCL efficacy analysis set. The majority of subjects 60/74 (81%) had a non-PD assessment by the IRC due to the follow up by CT scan alone after achieving CMR. Eleven subjects had a non-PD assessment due to other reasons. These included having a PET at an unscheduled time point, it was not evaluable, or it was not done.

Reviewer Comment:
The first PET required by protocol was on Day 29. Subjects who had a non-PD assessment at an unscheduled time point (prior to D29) either had an additional assessment at D29 or they died prior to D29. In the latter case, then the BOR was a non-PD. For some subjects, a PET scan was not performed at later time assessments (eg. D180, D270). In the case that the subject did not have progression or death prior to the data cutoff, then the DOR was censored at the date of the last adequate disease assessment. Many of these subjects, had a CR, and no subsequent PET. For those where response is not durable, a subsequent PET would have been informative, but ultimately will not change the DOR significantly as these evaluations are done monthly.
As per medical practice, CT alone is usually done for follow up of DOR and use of PET for surveillance purposes is discouraged for lymphoma.

In the leukapheresed DLBCL cohort, there were 108 subjects for whom an adjudication was needed. Within the JCAR017 Efficacy Set, an adjudication was needed for 91 (35.5%) of 256 subjects.

There were 15 subjects that were discordant based on BOR from PET staging; two were discordant based on DOFR from PET staging; 31 were discordant based on DOP from CT staging; nine discordant based on DOP from PET staging, 12 that were discordant based on DOP from CT staging and DOP from PET staging; eight that were discordant based on BOR from PET staging and DOFR from PET staging; three that were discordant based on BOR from PET staging and DOP from CT staging; five discordant based on BOR from PET staging and DOP from PET staging, two discordant based on BOR from PET staging, DOP from PET staging and DOFR from PET staging; one discordance based on BOR from PET staging, DOP from PET staging and DOP from CT staging; three discordant based on all 4 criteria.

Adjudication and re-adjudication of these 91 subjects provided further clarity and justified response assessments.

Reviewer Comment: Based on the 15 cases that were discordant for BOR from PET staging, it was noted the adjudicator picked the best response in the majority of the cases (10/15 [67%]). The Applicant provided additional adjudicator comments that justified their response assessment for the discordant cases as this detailed justification was not submitted in the CRF for each subject.

91 adjudicator comments were assessed. Review and verification of these efficacy assessments required manual review of multiple data points for each time point of assessments with each subject having multiple time points to be assessed.
and 12 subjects were noted to not have additional adequate information that would justify one radiologists' response assessment over another and therefore these response assessments could not be accurately evaluated. The response assessments had issues due to subjectivity with the use of visual interpretation in determining the Deauville score as opposed to the Lugano criteria which relies on SUV of the lesion and the liver.
Based on this, the FDA sent an IR to the applicant with a follow up telecon raising this review issue that in a single arm trial, the use of visual interpretation may introduce bias.

FDA requested re-adjudication of a subset of 12 subjects with justification for response, where discordance occurred for Best Overall Response from PET-staging

Re-adjudication provided a clearer and well justified response for the subjects in question, where BOR could have changed. Ultimately, all the response assessments were evaluated and unchanged based on clarity from the detailed adjudicator response and a re-adjudication with a detailed justification of the chosen response assessment.

Results of the primary endpoint analysis are show below:
The primary efficacy endpoint was ORR (null hypothesis of ORR ≤40%)
CR (null hypothesis of Cr rate ≤20%)

Table 10: Efficacy Analysis

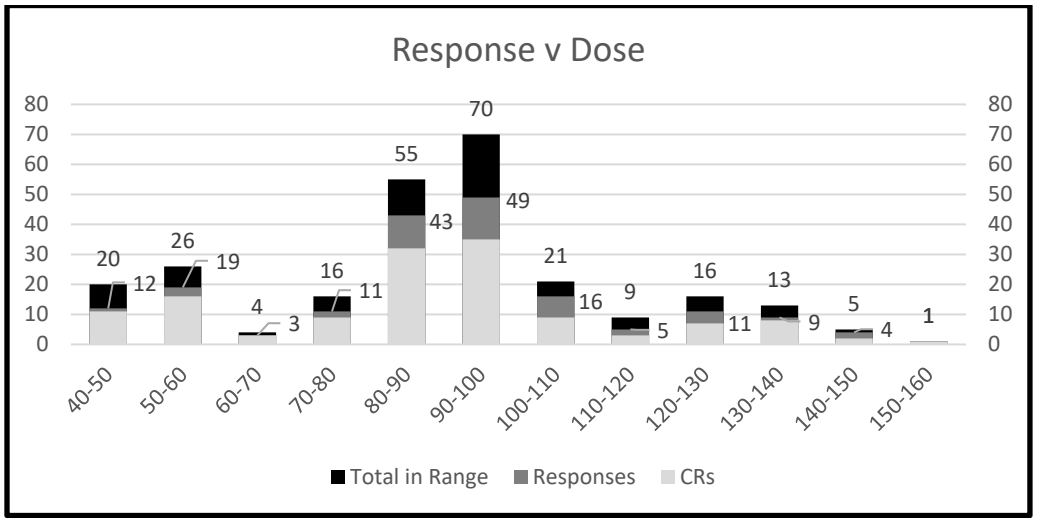
	Leukapheresed set, n=344	Treated analysis set, n=269	DLBCL Efficacy set, n=256	Dose range 50 -110 x 10^6 , n=192
ORR (CR+PR), n (%)	203 (59.0%)	190 (70.6%)	183 (71.5%)	141 (73.4%)
95% CI	(53.6%, 64.3%)	(64.8%, 76.0%)	(65.5%,76.9%)	(66.6%,79.5%)
Complete response rate, n (%)	148 (43.0%)	140 (52.0%)	136 (53.1%)	104 (54.2%)
95% CI	(37.7%, 48.4%)	(45.9%, 58.1%)	(46.8%,59.4%)	(46.8%,61.4%)
Partial response rate, n (%)	55 (16.0%)	50 (18.6%)	47 (18.4%)	37 (19.3%)
95% CI	(12.3%, 20.3%)	(14.1%, 23.8%)	(13.8%,23.7%)	(13.9%,25.6%)
Stable disease, n (%)	27 (7.8%)	24 (8.9%)	24 (9.4%)	15 (7.8%)
Progressive disease, n (%)	49 (14.2%)	42 (15.6%)	40 (15.6%)	30 (15.6%)
Non-progressive disease, n (%)	8 (2.3%)	7 (2.6%)	3 (1.2%)	0
Not evaluable, n (%)	57 (16.6%)	6 (2.2%)	6 (2.3%)	6 (3.1%)

In the DLBCL Efficacy set of 256 subjects, 183 subjects (71.5%) had a best overall response of CR or PR. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR was 65.5% which is well above the pre-specified null hypothesis rate of

40%. Among the 183 responders, 136 subjects (53.1%) had a best response of CR, and 47 (18.4%) subjects had a best response of PR.

The response versus dose assessment is below:
The number above the chart indicates how many subjects were in the dose range. The number next to the red bar represents all responses (CR+PR) and the green bar represents only the CRs.

Figure 2 Response versus Dose Assessment



Reviewer Comment: In the label, the applicant recommends a target dose of 100 × 10^6 CAR+ T cells. Most subjects received between 80-100 × 10^6 CAR+ T cells, as shown below. The mean (SD) dose given was 90 (25)× 10^6 CAR+ T cells . However, the dose range given to subjects was 40-160 × 10^6 CAR+ T cells, which is a wide range.

Statistical analyses were used to identify a more appropriate dose range that was efficacious. This analysis parsed out the dose range and evaluated the efficacy at the smaller dose range subset. The rows highlighted show that the lower bound of the 95% CI do not meet the success criteria of 40% which included the <50 dose, and doses above 110.
Not meeting the lower bound of 40% is likely due to the small sample size in those dose ranges where there is a paucity of efficacy data.

The statistical team was consulted about the post hoc groupings of dose by 10 rather than any other value (eg. 20/25). The narrower the dose grouping (e.g. 5), the scarcer data within each subgroup; the broader the grouping, the less informative this analysis becomes. Thus, the grouping of dose by 10 seems to be a reasonable tradeoff value for this descriptive subgroup analysis. The statistical team agreed that the dose interval length was reasonable. Since subjects assigned at dose 50 or 100 could potentially get a dose of 80 x 10^6 CAR+ T cells, it was agreed to tighten the dose range for analysis to determine if there was a difference in efficacy. Based on the given data, grouping the 60-70 x 10^6 CAR+ T cells could have also potentially decreased the lower bound from 50-70 or 60-80 x 10^6 CAR+ T cells analysis because of the small sample size. By this analysis, it is reasonable to exclude the 40-50 x 10^6 CAR+ T cells dose range as it fell below the null rate and the trial targeted subjects to receive a dose of 50 x 10^6 CAR+ T cells.

Based on these findings, this reviewer determined that that dose range should not include the lower (below 50) and higher range of dose (above 110), as there is a limited sample size to demonstrate efficacy. Although the dose range of 60-70 x10^6 CAR+T cells had limited sample size such that the lower bounds of the 95% CI were below the proposed null, this efficacy of this dose range was based on extrapolation of the efficacy observed in dose ranges below and above this dose range.
The dose on the label should encompass the dose range between 50-110 × 10^6 CAR+ T cells and not only the target dose of 100 × 10^6 CAR+ T cells, since there is efficacy above and below this target dose.

Table 11: Dose Range and Response

Dose Range	Subjects in Range	All Responses (CR+PR)	Response Lower Bound 95% CI
40-50 x 10^6	20	12	36.1
50-60 x 10^6	26	19	52.2
60-70 x 10^6	4	3	19.4
70-80 x 10^6	16	11	41.3
80-90 x 10^6	55	43	67.2
90-100 x 10^6	70	49	59.2
100-110 x 10^6	21	16	52.8
110-120 x 10^6	9	5	21.2
120-130 x 10^6	16	11	41.3
130-140 x 10^6	13	9	38.6
140-150 x 10^6	5	4	28.4
150-160 x 10^6	1	1	25

6.1.11.2 Analyses of Secondary Endpoints

Duration of Response for the DLBCL Efficacy Set is as below:

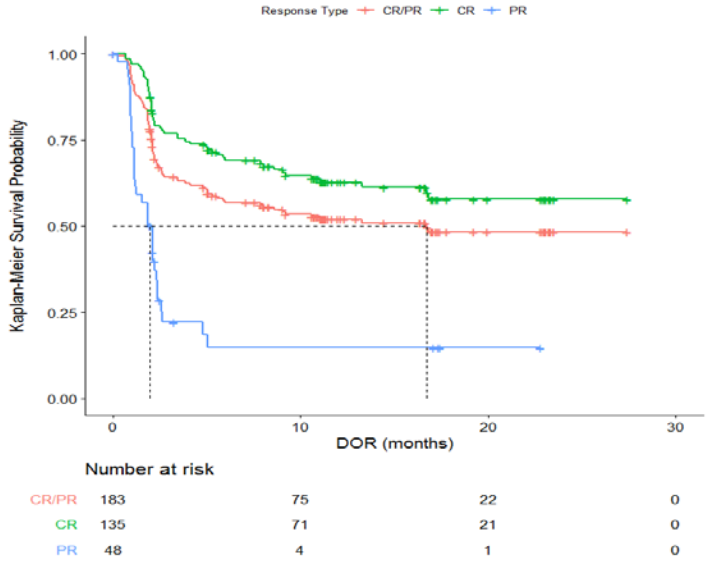
Table 12: Duration of Response

	DLBCL Efficacy Set, n=256	Dose range 50 -110 x 10^6, n=192
Number of subjects achieved CR or PR, n	183	141
Number of events, n (%)	85 (46.5%)	66 (46.8%)
Progression	83 (45.4%)	64 (45.4%)
Death	2 (1.1%)	2 (1.4%)
Censored, n (%)	98 (53.5%)	75 (53.2%)
Ongoing	59 (32.2%)	47 (33.3%)
Completed the Study	24 (13.1%)	18 (12.8%)
Received a new anticancer therapy	13 (7.1%)	9 (6.4%)
Proceeded to HSCT	2 (1.1%)	1 (0.7%)
DOR (months)		

median	16.7	16.7
95% CI	(6.0, NR)	(6.0, NR)
Follow up (months)		
median	12.9	16.4
95% CI	(11.3, 17.0)	(11.7, 17.0)

For the DLBCL Efficacy Set, the overall median was 16.7 months with a 95% limit of 6.0 months and an unattainable upper limit. The median follow-up time was 12.9 months (95% CI: 11.3, 17.0). For the subjects in the recommended dose range 50 - 110 $x10^6$ CAR+ T cells, the overall median DOR was 16.7 months with a lower 95% limit of 6.0 months and an unattainable upper limit. The median follow-up time was 16.4 months (95% CI: 11.7, 17.0).

Reviewer Comment:
The median DOR appears to be skewed upward because of the effect of the few outliers with durable remissions. Based on the Kaplan Meier curve below, every 6 months, approximately half of the population is censored. Based on this, most subjects are censored for DOR or relapse before 13 months. If all censored subjects were marked as failures (a worst case scenario), then the median DOR calculation was 6 months for all 141 responders with a 95% CI of 3.3, 11.1). Therefore, this verifies that the median DOR is inflated. To address this in labeling, the DOR for the leukapheresed set is being removed, as this population is a mixture of subjects who received conforming and nonconforming products and patients who never received the drug. Censor marks were placed in the labeling for median DOR for the responders within the dose range. Censor marks specifically were added for the DOR ranges, as the median DOR for all responders is inflated. There was internal disagreement on whether the median DOR of all responders should be completely removed, as these values were inflated. To omit this from the label would set a new precedent, as all other recently approved labels state the median DOR for all responders. This reviewer agreed to keep this in the label with the appropriate censor marks to denote a censored value. The table of the median follow up for DOR was removed, as the heavy censoring before 13 months contributes to the uncertainty in the follow up.



Source: Statistical Reviewer Analysis

Complete responders tended to have substantially longer DOR than the partial responders. In the DLBCL Efficacy Set, the median DOR for the partial responders was 2.0 months (95% CI: 1.2, 2.4) and the median DOR was not reached for complete responders (95% CI: 16.8, NR), leading to the median DOR for the complete responders and partial responders combined group as 16.7 months with an unattainable upper limit.

For analysis of PFS (n=256), the overall median was 3.5 months with a lower 95% limit of 3.0 months and an upper limit of 8.8 months. The median follow-up time was 12.8 months (95% CI: 12.1, 17.7).

For overall survival (n=256), a total of 116 subjects (45.3%) died in the DLBCL Efficacy set (n=256). The overall median survival time was 21.1 months with a lower 95% limit of 13.3 months and an unattainable upper limit. The median follow-up time for OS assessment was 17.5 months (95% CI: 13.2, 17.9).

6.1.11.3 Subpopulation Analyses

Subjects with secondary CNS lymphoma were included in the Efficacy Set.
Six subjects were included in the efficacy evaluable set. Three of the six subjects had CRs and were within the recommended dose range of 50-110 CART cells.
Of the three subjects with responses:
One had a with DOR of 16.8 months, received IT chemotherapy, had leptomeningeal disease, with a negative baseline CSF, a follow up CSF was not done and no disease present on MRI at D450
The second subject had a DOR of 1.9 months and progressed and then died. This patient received IT chemotherapy, had leptomeningeal, with a negative baseline CSF, follow up of the CSF was negative x3 and had no disease on MRI at D30.
The third subject had a DOR of 23.3 month. Received no IT chemotherapy; received radiation and had a dural and R posterior fossa mass (neither leptomeningeal or parenchymal disease), CSF studies were unknown, and the D90 CT was negative for disease.

Reviewer Comment: The review team considered broadening the indication statement to include patients with CNS disease by extrapolating data from the response of those with secondary CNS lymphoma. The sample size of 7 subjects is consistent with the CNS involvement in the eligible population. However, the data did not provide assurance that CART therapy alone had activity in the CNS particularly since baseline assessments following IT chemotherapy or radiation did not include baseline assessment of the disease prior to administration of CAR T therapy. The data is useful in providing prescribers with the safety and feasibility of using bridging therapy with IT chemotherapy and radiation therapy in conjunction with CAR T cell therapy with the investigational product

6.1.11.4 Dropouts and/or Discontinuations

Table 13: Discontinuations

Leukapheresed set, n (%)	**344 (100%)**
Discontinued before JCAR017 treatment	75 (21.8%)
Death	33 (9.6%)
Disease-related complication	6 (1.7%)

No longer meet eligibility criteria	5 (1.5%)
Manufacturing failure	27 (7.8%)*
Withdrew content	2 (0.6%)
Others	2 (0.6%)
JCAR017 treated	**269 (78.2%)**
Complete the study	35 (10.2%)
Follow-up ongoing	103 (29.9%)
Death	121 (35.2%)
Withdrew consent	7 (2.0%)
Lost to follow-up	2 (0.6%)
Others	1 (0.3%)

* 25 subjects received the non-conforming product

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

The key materials used for the safety review included:

- The BLA application electronic submission
- Applicant submissions in response to the review team's information requests
- Proposed labeling for KTE-X19
- Published literature
- Prior regulatory history

The clinical review of safety was primarily based upon analysis of 268 subjects in the DLBCL cohort (large B-cell lymphoma cohort) in study 017001 at the primary data cutoff of April 12, 2019. The JCAR017 analysis datasets (ADaM datasets) were used for the safety analysis. Analyses by the clinical reviewer for safety were performed using JMP 14. All narratives and relevant case report forms (CRFs) were reviewed for all serious adverse events (SAEs) and deaths that occurred in the primary safety population. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0, and AE severity was graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) severity was graded as a syndrome according to a modification of the 2014 Lee criteria grading system.[11] The modification of the Lee criteria is that neurologic AEs were not taken into account in CRS grading of organ toxicity since neurologic toxicity is now considered a distinct entity. Some AEs are presented throughout this review as grouped terms as defined by the review team. The complete list of FDA's grouped terms is presented in APPENDIX A. Unless otherwise specified, all analyses and tables were generated by the FDA clinical reviewer and/or the safety review team.

The safety analysis set included all subjects treated with any dose of JCAR017 product. The term JCAR017 or JCAR017 product in this review refers to conforming product unless otherwise specified. All AEs were collected from the start of leukapheresis until 90 days after JCAR017 infusion. Serious adverse events (SAEs) were defined as any AEs that met at least one of the following criteria: fatal, life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, resulted in congenital anomaly or birth defect, or resulted in any other

medically important serious event. SAEs were collected from the time of screening. Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring after initiation of JCAR017 administration through and including 90 days after final cycle of JCAR017. Majority of the 268 subjects received a single dose of JCAR017; 6 subjects were treated on the two-dose schedule at dose level 1 and 2 combined. Any AE occurring after JCAR017 retreatment (defined as administration of JCAR017 after progressive disease documentation following complete response) or start of another, subsequent anticancer therapy was not considered a TEAE. The 5 adverse event reporting periods with the data collected during these periods is shown in Table 14. Within the time periods, AEs were mapped as follows: i) Screening to the day before leukapheresis ii) leukapheresis to day before lymphodepleting chemotherapy (LDC) iii) start of LDC to day before 1st JCAR017 infusion iv) JCAR017 first infusion to and including 90 days (TEAE) v) posttreatment-emergent period to include AEs after 90 day, following JCAR017 retreatment or subsequent anticancer therapy. As of amendment 3, the following AEs were to be reported as SAEs from time of lymphodepleting chemotherapy: secondary malignancies, new onset or exacerbation of pre-existing-neurologic, rheumatologic or autoimmune disorder, new onset of hematologic disorder and rare and unexpected disorders with an unknown etiology e.g. Guillain-Barre syndrome.

Table 14. Adverse Event Reporting Periods in Study 017001

Time Period	Events to Record
Informed consent to start of LDC	Only AEs/SAEs related to protocol mandated procedures
Start of LDC to 90 days following final JCAR017 infusion or to EOS visit, whichever is earlier	All AEs/SAEs collected including AEs ongoing at start of LDC
Subjects with subsequent non-chemotherapy-containing anticancer therapy (e.g. checkpoint inhibitors) from day 61 to 90	All AEs/SAEs were collected for 30 days following start of new anticancer therapy even if this period extended beyond 90 days following final JCAR017 infusion
Subjects with subsequent chemotherapy containing anticancer therapy within 90 days	Only AEs/SAEs related to JCAR017 and/or protocol-mandated procedures were collected after initiation of subsequent anticancer therapy
91 days following JCAR017 infusion to EOS	Only AEs/SAEs related to JCAR017 and/or protocol-mandated procedures were collected

Source: Adapted from Table 4 of Applicant's Clinical Study Report
Abbreviations used: LDC: lymphodepleting chemotherapy, AEs: adverse events, SAE: serious adverse events EOS: end of study

Clinical reviewer comments

- *We defined AEs occurring after the start of JCAR017 infusion, regardless of perceived relationship with the investigational product, as adverse drug reactions (ADRs). Adverse events are reported by the applicant's preferred term, which may underestimate some AEs. To minimize underestimation of AE events, FDA grouped preferred terms that represent the same disease process. The reviewer utilized a grouping strategy for comprehensive analyses of AEs that is consistent*

with the grouping practices for review of similar agents within this class of therapies. Please refer to APPENDIX A for the full list of FDA's grouped terms

- *The 120-day safety update with data cutoff of August 12, 2019 had one additional patient in the safety analysis; no new safety signals were identified in this update*

- *Since immunomodulatory drugs e.g. checkpoint inhibitors, lenalidomide etc. may modulate T-cell expansion and function, as of amendment 4, all AEs/SAEs were collected of 30 days after initiation of such therapy following JCAR017 infusion. This requirement did not apply to chemotherapy as subsequent anticancer therapy following JCAR017 infusion since chemotherapy was not thought to affect CAR-T cell expansion and function in a manner similar to immunomodulatory agents*.

The demographic information and subject disposition for the subjects evaluated for safety are summarized in tables 15 and 16 below.

Table 15. Demographics of Safety Population in Study 017001

Demographics	DL1S N = 45 n (%)	DL2S N = 176 n (%)	DL3S N = 41 n (%)	DL1D N = 5 n (%)	DL2D N = 1 n (%)	Overall N = 268 n (%)
Age (years)						
< 65	30 (67)	108 (61)	18 (44)	2 (40)	1 (100)	159 (59)
≥ 65	15 (33)	68 (39)	23 (56)	3 (60)	0	109 (33)
< 75	41(91)	162 (92)	33 (80)	5 (100)	1 (100)	242 (90)
≥ 75	4 (9)	14 (8)	8 (20)	0	0	26 (10)
Mean (SD)	58 (14)	59.5 (13)	64 (13)	63 (8.5)	58 (0)	59.9 (13.3)
Median (range)	60 (20-82)	63 (18-79)	66 (32-86)	65 (52-73)	58 (58-58)	62 (18-86)
Sex						
Male	31 (69)	117 (66)	21 (51)	4 (80)	1 (100)	174 (65)
Female	14 (31)	59 (34)	20 (49)	1 (20)	0	94 (35)
Race						
White	41 (91)	148 (84)	36 (88)	5 (100)	1 (100)	231 (86)
Black	2 (4.4)	9 (5)	1(2.4)	0	0	12 (4.5)
Asian	1 (2.2)	9 (5)	1(2.4)	0	0	11 (4.1)
Multiple	1 (2.2)	0	0	0	0	1 (0.4)
American Indian or Alaska native	0	2 (1.1)	0	0	0	2 (0.7)
Not reported	0	8(4.5)	3 (7)	0	0	11 (4.1)
Ethnicity						
Not Hispanic or Latino	42 (93)	152 (86)	33 (80)	5 (100)	0	232 (87)
Hispanic or Latino	2 (4.4)	20 (11)	4 (10)	0	0	26 (10)
Unknown	1 (2.2)	4 (2.3)	4 (10)	0	1 (100)	10 (3.7)
Country						
USA	45 (100)	176 (100)	41 100)	5 (100)	1 (100)	268 (100)

Source: FDA analysis of adsl.xpt

The number of prior chemotherapy regimen subjects received prior to enrollment in the study 017001 in the JCAR017 treated set is listed in Table 17. All subjects were required to have received at least 2 prior lines of systemic therapy that included an anti-CD20 agent and an anthracycline. Ninety subjects (34%) received prior autologous stem cell transplant (ASCT). Most subjects were refractory to their recent prior treatment (212/268;79%) and 67% (180/268) were chemo-refractory. Seven subjects (2.6%) had central nervous system (CNS) involvement with lymphoma at first JCAR017 infusion.

Table 16. Subject disposition in safety population in study 017001

Disposition	DL1S N = 45 n (%)	DL2S N = 176 n (%)	DL3S N = 41 n (%)	DL1D N = 5 n (%)	DL2D N = 1 n (%)	Overall N = 268 n (%)
End of Study Status						
Discontinued	23 (51)	86 (49)	10 (24)	3 (60)	0	122 (46)
Completed	14 (31)	7 (4)	0	2 (40)	1 (100)	24 (9)
Ongoing	8 (18)	83 (47)	31 (76)	0	0	122 (46)
Reason for Discontinuation from Study						
Death	21 (47)	82 (47)	8 (20)	3 (60)	0	114 (43)
Withdrew Consent	2 (4.4)	2 (1.1)	2 (4.9)	0	0	6 (2.2)
Lost to follow up	0	2 (1.1)	0	0	0	2 (0.7)

Source: FDA analysis of adsl.xpt

Majority of deaths were due to progressive disease. Please see section 6.1.12.3 Deaths for details.

Table 17. Prior lines of therapy in study 017001

Characteristic	DL1S N = 45 n (%)	DL2S N = 176 n (%)	DL3S N = 41 n (%)	DL1D N = 6 n (%)	Overall N = 268 n (%)
Mean (SD)	3.3 (1.43)	3 (1.43)	2.4 (0.71)	3.2 (1.47)	3 (1.36)
Median	3	3	2	3.5	3
Min, max	1, 8	1, 8	1, 4	1, 5	1, 8
1	1 (2.2)	6 (3.4)	1 (2.4)	1 (16.7)	9 (3.4)
2	14 (31)	80 (45.5)	26 (63%)	1 (16.7)	121 (45)
3	12 (27)	45 (26)	10 (24)	1 (16.7)	68 (25)
4	11 (25)	26 (15)	4 (10)	2 (33)	43 (16)
≥5	7 (16)	19 (11)	0	1 (16.7)	27 (10)

Source: Adapted from Applicant analysis; Table 24 Clinical study report study 017001
**Applicant has 6 subjects in DL1D dose regimen; FDA notes 5 subjects (see comments below)*
Abbreviations used: DL1S, DL2S, DL3S: dose levels 1, 2 & 3 respectively, single dose
DL1D: Dose level 1, two-dose

Clinical Reviewer Comments

- *Study 017001 enrolled a fairly refractory large B-cell lymphoma population. Approximately 3% (9/268) of subjects did not meet study criteria of having to receive 2 prior lines of systemic therapy prior to enrollment. Maximum prior lines of therapy are eight.*

- *Applicant has 6 subjects in the dose level 1, two-dose JCAR017 dose regimen; our analysis has 5 subjects in this dose regimen and 1 subject in dose level 2, two-dose (DL1D) JCAR017 dose regimen. The Applicant did not open a DL2D cohort, but 1 subject was mistakenly given twice the DL1D dose and hence classified under DL2D. Since this is a minor discrepancy and the two-dose schedule subjects constituted a small minority (6/268; 2%) of patients analyzed for safety, without any major change in the outcomes analyzed, we decided to accept the Applicant's analysis in this instance.* 6.1.12.2

6.1.12.2 Overview of Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) were evaluated during clinic visits, hospitalizations, and follow-up visits per protocol-defined guidelines. Safety data are available for a total of 268 subjects who received JCAR017 before the data cutoff of 12 April 2019. Adverse events and deaths were also assessed for the period from enrollment to the planned time of infusion to assess risks for subjects who did not receive JCAR017 due to manufacturing issues or adverse events. Three hundred and forty-two subjects were in the leukapheresed set in the DLBCL cohort in study 017001. Of these 342 subjects, 50 did not receive JCAR017 (conforming or non-conforming) infusion. Reasons for not being treated with JCAR017 product included death (n=33), disease related complications (n=6), subjects no longer meeting eligibility criteria (n=3), withdrawal of consent (n=2), other (n=2) and inability to manufacturing product. Of the 292 subjects proceeding to JCAR017 infusion, 24 subjects received non-conforming product. For the safety review, "Day 1" refers to the day of JCAR017 infusion, and some AEs are presented as grouped terms. The applicant used preferred terms and grouped certain terms to present adverse reactions, but the grouping used was limited and occasionally missed cases. For a more comprehensive evaluation of safety, the clinical reviewer's analysis included grouped AEs that represented the same or similar clinical conditions. Examples are listed below. Please refer to APPENDIX A for the full list of FDA's grouped terms.

Ataxia: ataxia, balance disorder, coordination abnormal, dysmetria, dyskinesia, gait disturbance, hand-eye coordination impaired

Renal failure: acute kidney injury, blood creatinine increased, renal failure, renal injury, chronic kidney disease.

Ninety-nine percent of subjects had at least one AE. AEs and SAEs are events that occurred after the administration of JCAR017. Table 18 presents an overview of all AEs.

Table 18. Summary of Adverse Events Study 017001

AE/SAE	DL1S N = 45 n (%)	DL2S N = 176 n (%)	DL3S N = 41 n (%)	DL1D N = 5 n (%)	DL2D N = 1 n (%)	Overall N = 268 n (%)
All-Grade AEs	44 (98)	176 (100)	40 (98)	5 (100)	1 (100)	266 (99)
Grade 3-5 AEs	36 (80)	138 (78)	32 (78)	5 (100)	0	211 (79)
Grade 3	12 (27)	47 (27)	15 (37)	1 (20)	0	75 (28)
Grade 4	22 (49)	84 (48)	16 (39)	4 (80)	0	126 (47)
AEs leading to death*	2 (4.4)	9 (5)	1 (2.4)	0	0	12 (4.5)
SAEs	16 (36)	83 (47)	20 (49)	3 (60)	0	122 (46)

Source: FDA Analysis using adae.xpt, adsl.xpt study 017001
**Excludes death from progressive disease*
AE: Adverse event/s; SAE: serious adverse event/s
DL1S, DL2S, DL3S: dose levels 1, 2 &3 respectively, single dose; DL1D, DL2D: dose levels 1& 2 respectively, two-dose

Table 19. All grade nonlaboratory adverse events occurring in ≥ 10% of subjects

Body System Organ Class AE	All Grades (%)	Grades 3 or Higher (%)
Cardiac disorders		
Tachycardia*	25	0
Gastrointestinal disorders		
Nausea	33	1.5
Diarrhea	26	0.4
Constipation	23	0
Abdominal pain*	21	3
Vomiting	21	0.4
General disorders and administration site conditions		
Fatigue*	48	3.4
Pain*,#	28	1.5
Edema*, #	20	1.1
Pyrexia	16	0
Chills	12	0
Immune system disorders		
Cytokine Release Syndrome	46	4.1
Hypogammaglobulinemia**	32	0
Infections and infestations		
Infections: pathogen unspecified	29	16
Bacterial infection*	13	5
Upper Respiratory Tract Infection*,#	13	0.7
Viral infection*	10	1.5
Metabolism and nutrition disorders		
Decreased appetite	28	2.6
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	37	2.2
Motor dysfunction#,*	10	1.1
Nervous system disorders		
Headache*	30	1.1
Encephalopathy*,#	29	9
Dizziness*	24	2.6
Tremor*	16	0
Peripheral neuropathy*	11	0
Aphasia*	10	2.2
Psychiatric disorders		
Insomnia	13	0.4
Delirium*	10	2.2
Anxiety	10	0
Renal and urinary disorders		
Renal failure*	11	3
Respiratory, thoracic and mediastinal disorders		
Cough*	23	0

Body System Organ Class AE	All Grades (%)	Grades 3 or Higher (%)
Dyspnea*	16	2.6
Skin and subcutaneous tissue disorders		
Rash*,#	13	0.4
Vascular disorders		
Hypotension*	26	3.4
Hypertension	14	4.5
Hemorrhage*	10	1.5

Source: FDA Analysis adae.xpt AE: adverse event, SOC: system organ class, PT: preferred term
** Includes grouped terms as detailed in APPENDIX A;*
 # Encompasses more than one system organ class
***Hypogammaglobulinemia incidence based on AE reporting and laboratory testing*

Clinical Reviewer Comments

- *All grade AEs occurring in 10% or more subjects in study 017001 are consistent with those seen with other anti-CD19 CAR-T products. These AEs reflect the toxicities of the investigational protocol including lymphodepletion with Fludarabine and Cyclophosphamide*
- *Although the AEs are presented by system organ class (SOC), some grouped terms include more than one SOC and are indicated with a # sign in Table 19 e.g. encephalopathy includes nervous system disorders and psychiatric disorders SOCs. We placed these group term AEs under the SOC with most representation in the data for that AE and/or clinically most appropriate e.g. pain in general disorders, rash under skin and subcutaneous disorders SOC, encephalopathy under nervous system disorders*
- *The grouped term of hemorrhage (see APPENDIX A for list of preferred and grouped terms) included catheter site hemorrhage, conjunctival hemorrhage, epistaxis, intracranial hemorrhage, hematoma, hematuria, pulmonary hemorrhage, retinal hemorrhage, vaginal hemorrhage. We included anatomical sites other than gastrointestinal hemorrhage under this group term. Epistaxis contributed to the largest number of subjects under this group term. We placed hemorrhage under the SOC of Vascular Disorders despite epistaxis being the most frequent hemorrhage since we felt that clinically this was a better SOC rather than Respiratory System disorders under which epistaxis falls.*
- *For analyses of infection by pathogen, we included the grouped term e.g. bacterial infection but also included infections under other terms for which the organism was specified e.g. streptococcal sepsis was included in the calculation of bacterial infection. This was reflected in the AE high level group term (AEHLGT) column in the JMP datasets Occasionally the AEHLGT column did not capture the group term of bacterial infection as outlined in the FDA group and preferred terms list. We captured these events by creating a separate column in the datasets termed "AEHLGT modified" that reflected these changes. Febrile neutropenia was included in the numerator for all grade and grade 3 and higher infections.*
- *Pain as a group term was ultimately not included in the label, since we thought it was too broad a category to provide meaningful information to clinicians.*
- *The incidence of hypogammaglobulinemia is a composite of events reported in the AE dataset and laboratory values of IgG < 500mg/dl following JCAR017 infusion. This information was obtained from the Applicant through an IR.*

- *The incidence of encephalopathy in Table 19 differs from that in the section on neurologic toxicity given that in table 19 is reflective of all reported events of encephalopathy whether or not it was adjudicated to be due to study product e.g. encephalopathy from sepsis was included. In the section on neurologic toxicity, only those events thought to be due to CAR-T cell toxicity were included.*

Adverse Events from Screening to Lymphodepleting Chemotherapy (LDC)
This period included AEs from informed consent until the day before leukapheresis and from the day of leukapheresis to the day before the start of the last LDC prior to the first dose of JCAR017. Overview of AEs during these 2 time periods are shown in Table 20.

Table 20. Adverse Events from Screening to Lymphodepletion in Study 017001

Parameter	Screening to Leukapheresis n(%)	Leukapheresis to Lymphodepletion n(%)
Total Number of Subjects	344	342
Any AE	94 (27)	192 (56)
Any Grade 3-4 AE	13 (3.8)	48 (14)
Any Grade 5 AE	0	1 (0.3)
Any SAE	2 (0.6)	20 (6)

Source: Adapted form Applicant analysis; Table 62 of Clinical Study Report for study 017001; includes subjects who received non-conforming product
Abbreviations used: AE: adverse event; SAE: serious adverse event

From screening to leukapheresis, the most common adverse event reported was fatigue in 3.5 % of subjects. Post-leukapheresis and prior to the start of LDC, the most frequently reported AEs in 5% or more of subjects were fatigue (8%; 27/342), constipation (6%; 20/342) and anemia (6%; 19/342) and peripheral edema (5%; 17/342). 1 subject died of sepsis post leukapheresis.

Adverse events in subjects who received bridging therapy
Overall rates to treatment-emergent adverse events (TEAEs) were similar between subjects who received bridging therapy (n=159) and those who did not (n=109). However, rates of all grade CRS or NT (Applicant identified cases) were higher in those who received bridging therapy versus (vs) those who did not (55% vs 36%). Differences in grade 3 and higher cytopenias between those who received bridging and those who did not were also noted (neutropenia: 64% vs 53%; anemia: 46% vs 25%; thrombocytopenia: 33% vs 17%). Please see Table 21 below for a summary of safety in those who received bridging therapy vs those who did not.

Table 21. Safety Summary of Bridging Therapy*

Safety Parameter	Bridging Therapy Yes N=159 (%)	Bridging Therapy No N=109 (%)
Any TEAE	158 (99)	108 (99)
≥ Grade 3 TEAEs	137 (86)	75 (69)
All grade CRS	81 (51)	32 (29)
Grade 3 or 4 CRS	22 (14)	7 (6)
Grade 5 CRS	0	0
All grade NT	53 (33)	27 (25)
Grade 3 or 4 NT	21 (13)	6 (5.5)
Grade 5 NT	0	0

Safety Parameter	Bridging Therapy Yes N=159 (%)	Bridging Therapy No N=109 (%)
Grade 3 or 4 infection	21 (13)	10 (9)
Grade 5 infection	2 (1.3)	0

Source: Applicant analysis; adapted from Table 71 in clinical study report
*Abbreviations: TEAE: treatment emergent adverse event; CRS: cytokine release syndrome; NT: neurologic toxicity, *Does not include FDA adjudicated CRS, NT*

Clinical Reviewer Comments

- *Subjects who went on to receive non-conforming product were included in the time period from screening to LDC*
- *Most (27 of 33) deaths after leukapheresis and prior to JCAR017 infusion were due to progressive disease; other causes included unknown (n=3), cardiogenic shock (n=1), sepsis (n=1) and bowel perforation (n=1)*
- *AEs from bridging therapy occurred in the interval between leukapheresis and bridging therapy*
- *Increased incidence and severity of treatment emergent cytopenias were noted in those who received bridging therapy which is expected.*
- *Table 21 does not include the 9 additional subjects with CRS and the 17 additional subjects with NT adjudicated by the FDA clinical reviewer. However, since most additional subjects had low-grade of these toxicities and the overall safety profile of the drug product is not changed, a separate analysis including these subjects was not carried out. The differences in low-grade CRS between those who received bridging therapy versus those who did not is not well explained. Possibilities include more endothelial damage from additional chemotherapy contributing to a higher baseline (prior to JCAR017) inflammatory milieu or infection contributing to cytokine elevation or the need for bridging therapy in itself and its relationship to tumor burden or tumor replication.*
- *Given small numbers of subjects with grade 3 and higher CRS, NT and infections in subjects who received bridging and those who did not, it is speculative to comment on the observed differences of higher number of these events in the subjects who received bridging and does not alter the safety profile of JCAR017. In clinical practice, many subjects with aggressive large B-cell lymphomas will require bridging chemotherapy for tumor control, and any observed difference in safety between those who receive bridging vs those who do not will not translate into any change in clinical practice*
- *Two of 3 subjects who died of NT and 4 of 5 subjects who died of infection pneumonia, sepsis, 1 progressive multifocal leukoencephalopathy) received systemic bridging therapy. One subject who died of sepsis received palliative radiation but no systemic bridging therapy. The single subject who died of CRS did not receive bridging therapy. Nine of 12 subjects with fatal ADRs received bridging therapy.*

Adverse Events from Lymphodepleting Chemotherapy (LDC) to JCAR017 infusion

The lymphodepleting AE period was calculated from the first day of the last LDC (in case subjects received more than 1 round of LDC) to the day prior to JCAR017 infusion. Two hundred and seventy of 296 subjects (numbers reflect those who received non-conforming

product as well) had an AE and 223 (75%) of those were deemed related to LDC. Table 22 gives a summary of AEs unrelated or related to LDC during this time period.

Table 22. Adverse Events in Lymphodepletion period in Study 017001*

Parameter	Lymphodepletion Period N=296 (%)
Any AE	270 (91)
Any grade 3-4 AE	112 (38)
Any grade 5 AE	0
Any SAE	25 (8)
Any AE related to LDC	223 (75)
Any grade 3-4 AE related to LDC	89 (30)
Any grade 5 AE related to LDC	0
Any SAE related to LDC	13 (4.4)

Source: Applicant analysis; adapted from Table 64 in clinical study report for study 017001
**Includes those who received non-conforming product*
Abbreviations: AE: adverse event; SAE: serious adverse event; LDC: lymphodepleting chemotherapy

Table 23. Adverse Events in ≥ 10% of subjects in Lymphodepletion Period in Study 017001*

Adverse Event	Lymphodepletion Period N=296 (%)
Nausea	112 (38)
Fatigue	85 (29)
Anemia	90 (30)
Constipation	66 (22)
Hypomagnesemia	45 (15)
Vomiting	44 (15)
Neutropenia	42 (14)
Pyrexia	41 (14)
Headache	38 (13)
Hypokalemia	37 (12.5)
Peripheral edema	34 (11.5)
Decreased appetite	33 (11)
Diarrhea	30 (10)
Thrombocytopenia	30 (10)

Source: Applicant analysis; adapted from Table 65 of clinical study report for study 017001
**Includes those who received non-conforming product*

Clinical Reviewer Comments

- *AEs following LDC and prior to JCAR017 infusion included subjects who went on to receive non-conforming product. Since the toxicity of LDC is not expected to be different prior to infusion of conforming or non-conforming JCAR017, a separate analysis on those who received conforming JCAR017 was not carried out*
- *A total of 292 subjects received JCAR017: 268 conforming product and 24 non-conforming-product. Therefore, it appears that 4 subjects underwent LDC but did not go on to receive JCAR017-conofrming or non-conforming. Reasons for subjects who underwent leukapheresis but did not get JCAR017 are listed in the*

clinical reviewer comments under Table 21 (Safety Summary of Bridging Therapy); the majority of such subjects died of progressive disease. But the specific disposition of 4 subjects who received lymphodepletion but did not receive JCAR017 (conforming or non-conforming) is not listed.

- *In the reviewer's analysis of neurologic toxicity, (see reviewer's comments following Table 38) 2 subjects were assessed by this reviewer as having encephalopathy attributable to the fludarabine based on the onset and clinical presentation. The label therefore includes a reference to these events in the discussion of neurotoxicity in Section 5.*

Adverse Events in Outpatient Setting

Subjects were considered to have received outpatient treatment if their first JCAR017 infusion day did not overlap with any hospitalization stays during the study. Twenty-five of 268 subjects (9%) were treated in the outpatient setting. All had TEAEs and 17 of 25 subjects (68%) had ≥ grade 3 events consisting mainly of neutropenia (44%; 11/25), anemia (40%; 10/25), thrombocytopenia (12%, 3/25) and febrile neutropenia (12%; 3/25). There were no Grade 5 TEAEs. Cytokine release syndrome occurred in 48% (12/25) with 1 subject having grade 3-4 CRS; NT occurred in 44% (11/25) with 2 subjects (8%) having grade 3-4 NT. Eighteen (72%) of these 25 subjects were subsequently admitted to the hospital at a median of 5 days following JCAR017 administration (range 3-22 days) with 1 subject requiring ICU admission.

Clinical Reviewer Comments

- *Applicant wanted to include "monitoring 2-3 times during the first week following infusion at a certified healthcare facility for signs and symptoms of CRS and neurologic toxicities" in section 2.2. of the label. Their rationale was that JCAR017 is similar to tisagenlecleucel (Kymriah) in terms of CAR-T expansion and therefore daily monitoring is not needed. We disagree and recommend daily monitoring for the first week at a certified healthcare facility given that majority of subjects in study 017001 were inpatient at time of JCAR017 administration and were monitored daily following JCAR017 administration till hospital discharge. Also, non-REMS certified facilities would not have the necessary training in recognition and management for CAR-T cell associated toxicities.*
- *Given administration of CAR-T therapy in the outpatient setting for this and other products, we did not mandate that JCAR017 be administered only in the inpatient setting.*
- *Symptoms e.g. fever that could be manifestation of CRS or febrile neutropenia were taken to be a manifestation of CRS if it occurred within 30 days of JCAR017 infusion and the clinical picture was not indicative of a clear alternative diagnosis.*

For safety overview in other populations e.g. subjects with secondary CNS Lymphoma, subjects receiving non-conforming product and those with retreatment, please see 9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered.

6.1.12.3 Deaths

One hundred and fourteen of the 268 DLBCL, JCAR017 treated subjects had died at time of data cutoff for BLA submission. Applicant adjudicated cause of death in these 114 subjects as follows:
Disease progression (n=99); adverse event (n=9); Other (n=3) and Unknown (n=3)
The nine fatal adverse events per the Applicant were: pulmonary hemorrhage, multiple organ dysfunction syndrome, diffuse alveolar damage, leukoencephalopathy, septic shock(n=2), progressive multifocal leukoencephalopathy, myelodysplastic syndrome (MDS) and cardiomyopathy.

Three deaths attributed by Applicant to disease progression had attribution changed to fatal AE by the clinical reviewer based on review of death narratives. Summary of deaths in study 017001 based on final FDA adjudication is shown in Table 24 below.

Table 24. Summary of deaths in study 017001

Death Statistic	Overall N = 268 n (%)
All Deaths	114 (43)
Disease Progression	96 (36)
Adverse Events	12 (4.5)
Other causes	3 (1.1)
Unknown cause	3 (1.1)
Fatal AEs ≤ 30 days after JCAR017	5 (1.7%)
Fatal AEs > 30 days after JCAR017	7 (2.6)

Source: FDA Analysis at April 12, 2019 data cutoff

Clinical Reviewer Comments

- *The reviewer reviewed all death narratives to confirm the cause of death. Relevant datasets and CRFs were reviewed as needed to reach a conclusion on cause of death. Disease progression was considered as cause of death when supported by imaging, biopsy, autopsy or other descriptive narratives of progression of underlying malignancy. However, presence of underlying malignancy on autopsy did not always result in adjudication of death as disease progression since certain adverse reactions e.g. neurotoxicity is a clinical diagnosis and evidence of malignancy does not rule out death from such an adverse drug reaction.*

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- *Of the 99 subjects who died of disease progression per Applicant, we adjudicated cause of death to be other than disease progression in 3 subjects: Grade 5 neurotoxicity (n= 2) and Grade 5 sepsis (n=1). Hence, the total number of fatal AEs is 12.*

Final FDA adjudication of fatal events including subjects whose cause of death was changed from disease progression to fatal AE are shown in Table 25 below:

Table 25. Summary of Fatal AEs in study 017001

USUBJID	Fatal Adverse Event	Assigned Dose Regimen	Study day of death
017001(b) (6)	Encephalopathy	DL1S	17
017001(b) (6)	Pulmonary hemorrhage	DL2S	33
017001(b) (6)	Pneumonia	DL2S	85
017001(b) (6)	Encephalopathy	DL2S	21
017001(b) (6)	CRS	DL1S	23
017001(b) (6)	Leukoencephalopathy	DL2S	71
017001(b) (6)	Sepsis	DL2S	45
017001(b) (6)	Septic shock	DL2S	7
017001(b) (6)	Cardiomyopathy	DL2S	7
017001(b) (6)	Progressive multifocal leukoencephalopathy	DL3S	53
017001(b) (6)	Myelodysplastic syndrome	DL2S	670
017001(b) (6)	Septic shock	DL2S	79

Source: FDA analysis

Clinical Reviewer Comments

- *Of the 9 fatal AEs per the Applicant, we adjudicated diffuse alveolar damage as Grade 5 cytokine release syndrome (CRS), leukoencephalopathy as Grade 5 neurologic toxicity (NT) and multiple organ dysfunction syndrome as Grade 5 pneumonia (see narratives below).*

- *Overall fatal AE rate was 4%*

- *Of the 3 fatal neurotoxicity events, 2 were attributed to study product and one was thought to be more likely due to Fludarabine in context of sepsis. No subject who died of fatal NT had secondary CNS lymphoma at time of JCAR017 infusion. Death due to CRS and cardiomyopathy were attributed to study product.*

- *Assigned dose regimen for the 12 subjects with fatal AEs is as follows: DL1S (2 subjects); DL2S (9 subjects) and DL3S (1 subject). Nine of 12 subjects with fatal AEs had received bridging therapy.*

- *Cause of death listed as "other" by applicant include stroke, pneumonia and diffuse intra-abdominal ischemia. None of these deaths was attributed to study product or the investigational protocol. We agreed with the Applicant's assessment in these cases*

Narratives of subjects who died of an AE are listed below.

Subject 017001-(b) (6) 79-year old white male with DLBCL transformed from follicular lymphoma who died on day 17 from neurotoxicity attributed to JCAR017. Had CRS days 3-7 post JCAR017 infusion. Had multiple neurologic symptoms starting day 3 that subsequently worsened. Intubated day 11 for Grade 4 NT. Became completely unresponsive on day 16 and died on day 17.

Subject 017001-(b) (6) 63-year old white make with high grade lymphoma (HGL) (double/triple hit with DLBCL histology) who died on day 31 from grade 5 pulmonary hemorrhage most likely from tumor in setting of thrombocytopenia. Grade 4 CRS diagnosed day 4 along with NT. Intubated day 6 for acute respiratory failure. Worsening renal failure day 9 and cardiomyopathy diagnosed day 910. Pleural effusion showed CAR-T proliferation. GI bleed day 22 confirmed with endoscopy. Day 31 patient re-intubated with bronchoscopy showing pulmonary hemorrhage. Autopsy showed widespread disease involving lung, GI tract. NT, CRS, cardiomyopathy, respiratory failure, GI bleed reported ongoing at death.

Subject 017001-(b) (6) 72-year old white male with HGL (double/triple hit DLBCL, NOS) died of Grade 5 pneumonia on day 85. Diagnosed with life threatening pneumonia and Grade 2 neutropenia on day 78. Had worsening shortness of breath and subsequently diagnosed with Grade 4 sepsis; multifocal lung infiltrates. Treated with multiple antimicrobial agents. Intubated with refractory hypoxemia; high suspicion for pneumocystis pneumonia. Bronchoscopy not possible due to unstable situation; had worsening of creatinine and subsequently died. Cultures negative. Primary problem appears to have been worsening respiratory failure due to bilateral pneumonia leading to death-hence pneumonia adjudicated as Grade 5. Grade 4 sepsis per narrative with no mention of resolution-considered ongoing. Multi-organ failure likely the result of ongoing sepsis.

Subject 017001-(b) (6) 68-year old male (race unknown, Hispanic ethnicity) with DLBCL who died on day 17 from neurotoxicity attributed to JCAR017. Had CRS days 9 to 13. Had symptoms of facial weakness on day 10 followed by encephalopathy day 11. Subsequently had multiple symptoms including confusion, disorientation, aphasia, lethargy, agitation-all of which are consistent with CAR-T mediated NT. Imaging and EEG negative. On day 16, subject was minimally responsive and was transitioned to comfort care. Autopsy showed presence of lymphoma in the body which was not unexpected given that he died on day 17 following product infusion. NT is a clinical diagnosis and we adjudicated the subject's death due to NT based on clinical presentation and lack of a good alternative explanation.

Subject 017001-(b) (6) 82-year old white male with DLBCL who died on day 23 from diffuse alveolar damage that we adjudicated as grade 5 CRS. He had streptococcal bacteremia on day 1 that resolved on day 3. On day 6, he developed fevers again with negative infectious disease work up and new findings on chest X-ray. He was treated with broad spectrum anti-bacterial and anti-fungal agents. Developed profound NT with decorticate posturing on day 7.and grade 3 encephalopathy on day 8. Received steroids with improvement to Grade 1 NT on day 14. On day 17, he developed increasing oxygen requirements and was diagnosed with diffuse alveolar damage (DAD) on day 18. He had worsening of neurologic symptoms on day 20 with subsequent improvement and then worsening. Respiratory status worsened and he was transitioned to comfort care and died. Autopsy showed lymphoma (expected) and diffuse alveolar damage few days/weeks old. Blood cultures negative during this time. Recurrence of fever and new findings on chest X-ray consistent with CRS diagnosis. Steroids administered for NT could have masked subsequent fevers. Cytokine markers (IL-6, IL-8, IFN-γ) elevated initially and then declined followed by a second rise starting day 15. Although post bacteremia acute respiratory

distress syndrome (ARDS) is in the differential diagnosis, CRS could not be ruled out. DAD has been described to be a CRS manifestation.

Subject 017001-(b) (6) 74-year old white male with DLBCL who died of Grade 5 NT likely Fludarabine induced leukoencephalopathy in context of sepsis on day 71. Diagnosed with leukoencephalopathy starting day 43 with progressive worsening. Symptoms followed JCAR017 administration-so difficult to attribute NT to JCAR017 versus Fludarabine. No evidence of lymphoma at autopsy and prior PET scan was negative for CNS lymphoma. Intravascular bacteria noted at autopsy indicative of antemortem bacteremia and patient had history of E.Coli urinary tract infection prior to death. Fludarabine considered more likely as cause of neurotoxicity given autopsy findings (axonal injury in bilateral optic radiations) and patient's elevated creatinine at baseline that increases risk of Fludarabine induced toxicity.

Subject 017001(b) (6) 67-year old white female with HGL (double/triple hit with DLBCL) who died day 45 of Grade 5 Sepsis in setting of disease progression and ongoing neurotoxicity. Subject had neurologic symptoms starting day 3 that subsequently worsened and reported ongoing at death. Grade 4 vancomycin resistant enterococcal bacteremia and Grade 4 systemic candida infection on day 30. PET scan on day 40 showed a mixed response with decreased uptake in certain areas and increased uptake/new lesions in other areas. Also noted to have cerebral infarction. Possibility of septic emboli is not ruled out. Although disease progression was noted, given systemic fungal, and bacterial infection resistant to antibiotics in the setting of profound neutropenia, that had not resolved at time of death, we adjudicated death as Grade 5 sepsis. LDH, a marker of tumor burden decreased from baseline making disease progression a less likely cause of death.

Subject 017001-(b) (6) 38-year old with high grade lymphoma (double/triple hit) with extensive tumor burden with grade 2 CRS on day 4 followed by grade 4 septic shock on day 5. Had culture positive bacterial UTI with 2 organisms (Staphylococcal aureus and Corynebacterium). Worsening tumor burden with massive retroperitoneal and pelvic adenopathy contributing to urinary tract obstruction was noted. Had cardiac arrest x 2 on day 7 and could not be resuscitated. Autopsy revealed high grade lymphoma with Burkitt lymphoma like features; post-mortem blood culture grew *Stenotrophomonas maltophilia.* Cause of death deemed to be sepsis shock in setting of massive tumor burden especially in the abdomen leading to urinary tract obstruction. CRS deemed ongoing at death.

Subject 017001-(b) (6) 51-year old American Indian female with DLBCL who died of cardiomyopathy attributed to study product on day 7. She was unresponsive on day 4 with pulseless electrical activity and ventricular fibrillation. Treated with cardiac medications and steroids. Subsequent Echocardiogram showed severe cardiomyopathy with ejection fraction (EF) of 20%. Echocardiogram prior to study product administration showed EF of 62%. EF further worsened to 15% and subject died on day 7 from non vaso-occlusive cardiomyopathy. Autopsy showed subendothelial necrosis in left ventricle and interventricular septum though there was no lymphocytic infiltrate in the myocardium. Death within a week of study product administration, normal EF prior to study product administration and no other cause for cardiomyopathy led us to adjudicate Grade 5 cardiomyopathy due to study product administration.

Subject 017001-(b) (6) 70-year old white female with DLBCL transformed from follicular lymphoma who died of progressive multifocal leukoencephalopathy (PML) on day 53. She had evidence of JC virus infection within 4 days of study product administration and died on day 53.

Subject 017001-(b) (6) 70-year old white male with DLBCL transformed form follicular lymphoma who died of MDS on day 670 despite treatment for MDS. He was diagnosed with Grade 3 MDS on day 336. No JCAR017 transgene detected on MDS tissue sample.

Subject 017001-(b) (6) 46-year old white male with DLBCL who died of sepsis in context of peripheral T cell lymphoma (PTCL) and DLBCL progression on day 79. He had skin biopsy from right forearm showing involvement with diffuse large B cell lymphoma (DLBCL) prior to JCAR017 infusion. Bone marrow biopsy prior to JCAR017 infusion showed atypical lymphohistiocytic infiltration with no evidence of DLBCL and moderate megakaryocytic dysplasia. Day 28 PET/CT showed marked disease progression and day 30 skin biopsies from multiple sites led to a diagnosis of PTCL, not otherwise specified (NOS). PTCL was tested for CAR-T transgene and it was concluded that the secondary T cell malignancy was derived from a non-CAR T cell. Subject had productive cough starting day 65 and was admitted day 72 with Grade 4 septic shock. CT showed multiple pulmonary and hepatic lesions, right renal mass, splenomegaly. Received multiple antimicrobial agents and anticancer therapy and was transitioned to palliative care. Death due to sepsis in setting of profound pancytopenia with progression of underlying DLBCL and PTCL.

6.1.12.4 Nonfatal Serious Adverse Events

For this review, SAEs were defined as any serious AE that occurred after the start of JCAR017 administration. SAEs occurred in 122 of 268 subjects (46%). Table 26 summarizes all SAEs and grade ≥ 3 SAEs.

Table 26. Nonfatal Serious Adverse events in ≥ 1% study subjects

Adverse Events	All Grades N (%)	Grade 3-4 N (%)
Cytokine Release Syndrome	49 (18)	8 (3)
Encephalopathy	33 (12)	16 (6)
Neutropenia	11 (4.1)	11 (4.1)
Sepsis	11 (4.1)	9 (3.4)
Pneumonia	9 (3.4)	7 (2.6)
Aphasia	9 (3.4)	3 (1.1)
Thrombocytopenia	10 (3.7)	10 (3.7)
Hypotension	8 (3)	6 (2.2)
Pyrexia	9 (3.4)	0
Febrile neutropenia	10 (3.7)	10 (3.7)
Gastrointestinal Hemorrhage	5 (1.9)	5 (1.9)
Dizziness	7 (2.6)	4 (1.5)
Delirium	6 (2.2)	4 (1.5)
Bacterial Infection	5 (1.9)	1 (0.4)
Anemia	5 (1.9)	5 (1.9)
Dyspnea	5 (1.9)	5 (1.9)
Renal Failure	5 (1.9)	4 (1.5)

Adverse Events	All Grades N (%)	Grade 3-4 N (%)
Paresis	3 (1.1)	2 (0.7)
Abdominal Pain	3 (1.1)	2 (0.7)
Tremor	4 (1.5)	0
Ataxia	3 (1.1)	0
Cardiac Arrhythmias	3 (1.1)	3 (1.1)
Pleural effusion	2 (0.7)	2 (0.7)
Cardiac Failure	2 (0.7)	1 (0.4)
Dehydration	3 (1.1)	2 (0.7)
Musculoskeletal Pain	3 (1.1)	2 (0.7)
Fatigue	3 (1.1)	2 (0.7)
Motor Dysfunction	2 (0.7)	1 (0.4)
Pain	2 (0.7)	1 (0.4)
Pericardial Effusion	2 (0.7)	2 (0.7)
Leukopenia	2 (0.7)	2 (0.7)
Dysphagia	2 (0.7)	2 (0.7)
Bile duct obstruction	2 (0.7)	2 (0.7)
Malignant pleural effusion	2 (0.7)	2 (0.7)
Hemorrhage	2 (0.7)	0
Tachycardia	2 (0.7)	0
Viral Infection	3 (1.1)	2 (0.7)
Thrombosis	2 (0.7)	1 (0.4)
Seizure	2 (0.7)	2 (0.7)
Cytomegalovirus Infection	1 (0.4)	1 (0.4)
Pancytopenia	1 (0.4)	1 (0.4)
Failure to thrive	1 (0.4)	1 (0.4)
Apnea	1 (0.4)	0
Female genital tract fistula	1 (0.4)	0
Upper Respiratory Tract Infection	1 (0.4)	1 (0.4)
Bone marrow failure	1 (0.4)	1 (0.4)
Cerebrovascular accident	1 (0.4)	0
Hypoxia	1 (0.4)	0
Small intestinal obstruction	1 (0.4)	0

Source: FDA Analysis of adae.xpt, adsl.xpt

Clinical Reviewer Comment

- *The label includes nonlaboratory SAEs ≥ 2%. The Applicant initially did not want to use grouped terms in this listing e.g. Applicant chose to keep confusional state and mental status changes while we grouped these terms under encephalopathy. However, since such a practice may result in under-reporting of events, we told them to use group terms and they accepted.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest for safety analyses included infusion reaction, cytokine release syndrome (CRS), neurologic toxicity (NT), macrophage activation syndrome (MAS), tumor lysis syndrome (TLS), hypogammaglobulinemia, prolonged cytopenias not resolved by day 29 post JCAR017 infusion, infections, secondary malignancies and autoimmune events.

Cytokine release syndrome (CRS)

CRS occurred in 122 subjects (46%), 11 (4%) of whom experienced grade 3 or higher CRS. One subject died of CRS (see 6.1.12.3 Deaths for details) and 2 subjects had CRS ongoing at time of death. Cause of death was pulmonary hemorrhage and progressive disease for the 2 subjects for whom CRS was reported as ongoing at time of death. Seventy-eight of 122 subjects (64%) with CRS had associated neurologic toxicity.(for analyses of subjects with both CRS and neurologic toxicities, please see neurologic toxicity in this section). CRS was graded per modified Lee et al 2014 criteria which excludes neurologic AEs as part of CRS.

Table 27. CRS Toxicity Grade

Worst CRS Toxicity Grade	Subjects N (%)
CRS Any Grade	122 (46%)
Grade 1	70 (26%)
Grade 2	41(15%)
Grade 3	6(2%)
Grade 4	4(1.5%)
Grade 5	1(0.37%)

Source: FDA Analysis of CRSPRIM Legacy Dataset

CRS grades across different dose cohorts in study 017001 were as shown in Table 28. Twenty-one percent (57 of 268 subjects) received tocilizumab and/or corticosteroids for management of CRS. Sixteen percent (30 of 268 subjects) received tocilizumab alone, 8% percent (22 of 268 subjects) received tocilizumab and corticosteroids while 2% (5 of 268 subjects) received corticosteroids only for CRS management.

Table 28. CRS in different dose cohorts in study 017001

JCAR017 Dose Cohort	Number of Subjects	CRS Grade 1-5 N (%)	CRS Grade 3-4 N (%)
Single Dose, Level 1	45	19 (42)	2 (4.4)
Single Dose, Level 2	176	73 (41)	8 (4.5)
Single Dose, Level 3	41	26 (63)	0
Two Dose, Level 1	5	4 (80)	0
Two Dose, Level 2	1	0	0

Source: FDA Analysis using adae.xpt, adsl.xpt

Median time to CRS onset was 5 days (range 1 to 15 days). CRS resolved in the majority (119 of 122, 98%) of subjects with a median time to resolution of 5 days (range 1 to 17 days). The median duration of CRS in all subjects including those who died from CRS or had CRS ongoing at death was 5 days (range 1 to 30 days). The median time to maximum CRS grade was 5 days (range 1 to 23 days).

The most common manifestations of CRS included fever (94%), hypotension (49%), tachycardia (39%), chills (28%), hypoxia (21%), fatigue (16%) and headache (14%). Other serious events associated with CRS include acute kidney injury, cardiac arrhythmias including atrial fibrillation, AV block, bradycardia, elevated hepatic aminotransferases,

respiratory failure including that due to diffuse alveolar damage. Tables 29 and 30 below summarize the AE and SAEs observed in subjects with CRS.

Table 29. Symptoms in 122 subjects with CRS

CRS Symptoms/AEs*	All grades n(%)	Grades 3 or higher n (%)
Total	122 (100.0)	24 (19.7)
Pyrexia	113 (92.6)	6 (4.9)
Hypotension	59 (48.4)	9 (7.4)
Tachycardia	47 (38.5)	0
Chills	34 (27.9)	0
Hypoxia	26 (21.3)	9 (7.4)
Fatigue	17 (13.9)	0
Headache	17 (13.9)	3 (2.5)
Nausea	8 (6.6)	0
Tachypnoea	7 (5.7)	1 (0.8)
Malaise	6 (4.9)	0
Dyspnea	5 (4.1)	2 (1.6)
Dizziness	3 (2.5)	0
Decreased appetite	2 (1.6)	0
Hyperhidrosis	2 (1.6)	0
Pain	2 (1.6)	0
Tremor	2 (1.6)	0
Acute kidney injury	1 (0.8)	1 (0.8)
ALT increased	1 (0.8)	0
Arthralgia	1 (0.8)	0
AST increased	1 (0.8)	0
Ataxia	1 (0.8)	0
Atrial fibrillation	1 (0.8)	1 (0.8)
Atrioventricular block	1 (0.8)	1 (0.8)
Bradycardia	1 (0.8)	0
Diffuse alveolar damage	1 (0.8)	1 (0.8)
Febrile neutropenia	1 (0.8)	1 (0.8)
Lethargy	1 (0.8)	0
Muscular weakness	1 (0.8)	0

CRS Symptoms/AEs*	All grades n(%)	Grades 3 or higher n (%)
Myalgia	1 (0.8)	0
Orthostatic hypotension	1 (0.8)	0
Pericardial effusion	1 (0.8)	1 (0.8)
Pneumonitis	1 (0.8)	1 (0.8)
Renal failure	1 (0.8)	1 (0.8)
Renal injury	1 (0.8)	0
Respiratory failure	1 (0.8)	1 (0.8)

*ALT: Alanine aminotransferase; AST: Aspartate Aminotransferase *Does not include grouped terms*
Source: Applicant analysis; response to information request #75

Table 30. CRS Serious Adverse Events (SAEs); N=49 of 122 subjects with CRS

CRS Symptoms/SAEs	All Grades n (%)	Grades 3 or Higher n (%)
Total CRS SAEs	49 (100.0)	17 (34.7)
Pyrexia	45 (91.8)	3 (6.1)
Hypotension	29 (59.2)	8 (16.3)
Tachycardia	26 (53.1)	0
Chills	16 (32.7)	0
Hypoxia	16 (32.7)	7 (14.3)
Fatigue	6 (12.2)	0
Dyspnea	5 (10.2)	2 (4.1)
Headache	5 (10.2)	2 (4.1)
Nausea	5 (10.2)	0
Malaise	4 (8.2)	0
Tachypnoea	3 (6.1)	1 (2.0)
Hyperhidrosis	2 (4.1)	0
Acute kidney injury	1 (2.0)	1 (2.0)
Ataxia	1 (2.0)	0
Atrial fibrillation	1 (2.0)	1 (2.0)
Atrioventricular block	1 (2.0)	1 (2.0)
Bradycardia	1 (2.0)	0
Decreased appetite	1 (2.0)	0
Diffuse alveolar damage	1 (2.0)	1 (2.0)

CRS Symptoms/SAEs	All Grades n (%)	Grades 3 or Higher n (%)
Lethargy	1 (2.0)	0
Muscular weakness	1 (2.0)	0
Myalgia	1 (2.0)	0
Pericardial effusion	1 (2.0)	1 (2.0)
Pneumonitis	1 (2.0)	1 (2.0)
Renal failure	1 (2.0)	1 (2.0)
Renal injury	1 (2.0)	0
Respiratory failure	1 (2.0)	1 (2.0)
Tremor	1 (2.0)	0

**No grouped terms used* *Source: Applicant analysis; response to information request #75*

CRS Management

Tocilizumab and/or corticosteroids were used in the management of CRS. Tables 31 and 32 depict the use of tocilizumab, corticosteroids and other interventions used in study 017001 in the management of CRS.

Table 31. Tocilizumab and/or Corticosteroid Use in CRS management

Medication	DL1S N=45 (%)	DL2S N=176 (%)	DL3S N=41 (%)	DL1D N=6 (%)	Overall N=268 (%)
Tocilizumab	4 (9)	37 (21)	11 (27)	0	52 (19)
Corticosteroids	6 (13)	20 (11)	8 (19.5)	0	34 (13)
Tocilizumab and Corticosteroids	3 (6.7)	17 (10)	5 (12)	0	25 (9)
Tocilizumab or Corticosteroids	7 (15.5)	40 (23)	14 (34)	0	61 (23)

Source: Applicant analysis; response to information request #83

Table 32. Other Interventions for Treatment Emergent CRS

Intervention	DL1S N=45 (%)	DL2S N=176	DL3S N=41 (%)	DL1D N=6 (%)	Total N=268 (%)
ICU Admission	1 (2.2)	6 (3.4)	0	0	7 (2.6)
Dialysis	1 (2.2)	1 (0.6)	0	0	2 (0.7)
Ventilator Use	1 (2.2)	3 (1.7)	0	0	4 (1.5)
Vasopressors	1 (2.2)	7 (4.0)	0	0	8 (3.0)

Source: Applicant analysis; response to information request #75

Clinical reviewer's comments

- *Applicant had identified only 113 subjects with CRS. Our review strategy of finding additional subjects with CRS included looking for fever, hypotension and hypoxia between day 1 to 30 in the subjects not flagged as having CRS. We additionally looked for subjects not flagged as having CRS with tocilizumab and vasopressor use. We did not look for corticosteroid use in subjects not flagged as having CRS given that corticosteroids are used for neurotoxicity as well which is a confounding factor. We looked at cytokine and laboratory data (Ferritin, C-reactive protein) for supportive evidence. After reviewing narratives on 46 subjects, we adjudicated 9 additional subjects as having CRS the details for whom are provided below. Although majority of the additional subjects identified with CRS had low grade events, we identified one fatal and one grade 4 event amongst the 9 subjects.*

Subject 017001-(b) (6) *Grade 2 CRS days 1-3 manifested by persistent hypotension for 3 days following JCAR017 infusion.*

Subject 017001-(b) (6) *Grade 1 CRS days 11-15 characterized by fever with no good alternative explanation.*

Subject 017001(b) (6) *Deemed to fatal CRS that started on day 6 with fever, new infiltrates on chest X-ray. Subsequently noted to have diffuse alveolar damage with death on day 23. Please see section* 6.1.12.3 Deaths *for details.*

Subject 017001-(b) (6) *Grade 2 CRS days 2-4 with fever and hypotension. Received tocilizumab on day 4. Had elevated IL-6, C-reactive protein and serum Ferritin levels. Applicant's explanation of CMV viremia as the cause did not fit in with time frame of symptoms and response to tocilizumab.*

Subject 017001-(b) (6) *Grade 1 CRS days 14-18. Had fever which resolved promptly with single dose of tocilizumab. Applicant explanation of fever due to underlying lymphoma or infection did not fit with given scenario.*

Subject 017001-(b) (6) *Grade 1 CRS days 15-16 following second dose of JCAR017 infusion on day 15. Had fever, tachycardia, tachypnea, chills, nausea, vomiting with no good alternate explanation. Also noted to have increased C-reactive protein and Ferritin.*

Subject 017001-(b) (6) *Grade 1 CRS day 2-3. Presented with fever with elevated IL-6, Ferritin and C-reactive protein. Applicant explanation of fever due to tumor burden does not fit given that fever was not reported during other periods of disease worsening and occurred shortly after JCAR017 infusion.*

Subject 017001-(b) (6) *CRS days 2-5 with maximum grade of 4. Subject had fever, grade 3 hypotension on day 2 followed by atrial fibrillation with subsequent intubation, mechanical ventilation and vasopressor treatment. Received tocilizumab during this period and responded. Timing and nature of symptoms consistent with CRS.*

Subject 017001-(b) (6) *Grade 1 CRS days 9-10. Subject presented with fever and responded to tocilizumab. Although febrile neutropenia was in the differential diagnosis, CRS could not be ruled out.*

- *CRS following retreatment was excluded from the analyses; in subjects with retreatment, CRS following the first infusion of JCAR017 was considered*

- *There was about a 20% increase in total number of CRS events in single dose level 3 cohort compared to dose level 2 or dose level 1, but no increase in Grade 3 or 4 events*

- *We analyzed median duration of CRS as median time to resolution in those for whom CRS resolved and as median duration of CRS in all subjects. We did this analysis in 2 ways since we wanted to convey to the treating physician that the vast majority of subjects had resolution of CRS and what to expect as a time frame for CRS resolution. However, we also want treating physicians to be aware of the possibility of CRS resulting in death or remaining ongoing at death*

- *Applicant defined time to resolution of CRS as number of days from onset to when the last CRS event of the first episode ends. Eight subjects had non-event days in between start and end day of CRS, but Sponsor included these in the CRS duration as confirmed in the CRSPRIM Legacy dataset and we agree with this approach given that ongoing symptoms during non-event days may not have been accurately captured.*

- *Applicant did not include end day of certain toxicities e.g. acute kidney injury (AKI) in the calculation of CRS resolution. CRS resolution was based on end day of systemic symptoms like fever, hypotension etc. Since the number of subjects with organ toxicity were small, we chose to describe subjects with organ toxicity separately in addition to their inclusion in general calculation for median time to CRS resolution. Eight subjects had organ toxicity associated with CRS. Organ toxicities included renal failure, respiratory failure, diffuse alveolar damage, pneumonitis, pericardial effusion, atrial fibrillation, complete atrioventricular block and aminotransferase elevation. Two of 8 subjects had more than one organ toxicity. One subject died from organ toxicity (diffuse alveolar damage) while 1 subject had unresolved toxicity of renal failure. Organ toxicities resolved in 6 subjects although in 2 subjects, toxicities were either not reported as resolved or reported as resolving/recovering. Review of narratives however show that organ toxicities resolved in these 2 subjects. Of the 6 subjects in whom organ toxicity resolved, 4 had resolution of organ toxicity following CRS resolution while in the remaining 2 subjects, organ toxicity resolved before or with CRS resolution. Median duration of CRS in these 8 subjects including the duration of organ toxicity is 8.5 days (4 to 69 days).*

- *Applicant assigned an incorrect grade to CRS in 6 subjects. We changed the grade in these subjects based on review of narratives, ADAE and ADCM datasets. We specifically looked at vasopressor and oxygen use in the ADCM dataset and grade 3 and higher organ toxicities in the ADAE dataset to identify subjects with a higher CRS grade than the one assigned. Details of these subjects are given below*

Subject 017001-(b) (6) *Applicant assigned grade 2 changed to grade 5. Please see section* 6.1.12.3 Deaths *for details.*

Subject 017001-(b) (6) *Applicant assigned grade 2 changed to grade 3 based on occurrence of grade 3 atrioventricular (AV) block days 9-13. AV block deemed as cardiac toxicity of CRS since arrhythmias are well known complications of CRS.*

Subject 017001-(b) (6) *Applicant assigned grade 2 changed to grade 3 based on oxygen administration of FiO2 > 40% during CRS.*

Subject 017001-(b) (6) *Applicant assigned grade 3 changed to grade 4 based on occurrence of grade 4 pneumonitis requiring mechanical ventilation and grade 4 acute kidney injury (AKI) during CRS. Pneumonitis and AKI are well known complications of CRS and hence the change in grade based on organ toxicity and the requirement for mechanical ventilation.*

Subject 017001-(b) (6) *Applicant assigned grade 2 changed to grade 4 based on need for mechanical ventilation in setting of atrial fibrillation. Atrial fibrillation attributed to CRS since arrhythmias are known complications of CRS.*

Subject 017001-(b) (6) *Applicant assigned grade 2 changed to grade 3 based on oxygen administration of FiO2 > 40% during CRS.*

- *Management of CRS with tocilizumab and/or corticosteroids as shown in Table 31 (denominator 268 subjects in study 017001) is consistent with clinical practice. Of the 122 subjects with CRS, tocilizumab was used in 52 (43%), corticosteroids in 34 (13%) and tocilizumab and/or corticosteroids in 61 (23%). Tocilizumab alone was used in 27 (10%) while corticosteroid alone was used in 9 (3%) of subjects with CRS.*
- *Initially (IR#75), the Applicant did not include subjects with CRS who received corticosteroids in the analysis of CRS management if the indication to receive corticosteroids did not include CRS. For example- if a subject received corticosteroids with the indication of CNS AE or for lymphoma, the subject was not labelled as having received corticosteroids for CRS despite the medication being given in the timeframe for CRS. However, steroids given for any indication during CRS irrespective of indication listed have the potential to impact CRS outcome. Hence, the Applicant reanalyzed the data and 7 additional subjects were adjudicated as having received corticosteroids for CRS. Ten other subjects with CRS received corticosteroids for either neurologic toxicity on the day CRS was adjudicated to have ended or for other reasons e.g. allergic reaction. These 10 subjects were deemed as not having received corticosteroids for CRS. On review of the narratives provided by the Applicant, the clinical reviewer agrees with the adjudication.*
- *In general, rate of grade 3 and higher CRS was low. Interventions like dialysis, ventilatory support, vasopressors and ICU stay as outlined in Table 32 were required in very subjects corresponding to the low rate of grade 3 and higher CRS. Lower rates of severe CRS is likely due to early recognition and intervention preventing serious toxicity and end organ damage. Comparison across similar products is difficult given evolving understanding in the pathophysiology and management of CRS and differences in study population*
- *The one subject with fatal CRS had diffuse alveolar damage (DAD) as the manifestation of CRS. This finding was added to the PI so that clinicians are aware*

of the possibility that CRS can manifest as DAD. Diffuse alveolar damage as a manifestation of CRS has been described in the published literature as well.

Neurologic Toxicity

FDA's neurotoxicity analysis was based on the MedDRA system organ classes and included all events from the nervous system disorders and psychiatric disorders that occurred, regardless of the applicant's attribution as "investigator identified neurologic toxicity" (iiNT) flag. The analyses captured events misclassified under other organ system classes and not captured by the applicant as neurologic (e.g., five subjects with events of blindness, blurred vision, gaze palsy and mydriasis that were part of neurologic toxicity were under "Eye disorders"). For the purpose of this review, certain AEs were grouped into a larger category (e.g., encephalopathy, delirium).

Ninety-five subjects (35%) experienced one or more events of neurologic toxicity (NT) including Grade 3 or higher events in 12% (31/268) of subjects. Three subjects had fatal neurologic toxicity with encephalopathy being the grade 5 event in all 3 subjects. Of the 3 subjects with fatal encephalopathy, 1 subject was deemed to have leukoencephalopathy most likely due to Fludarabine used in the lymphodepletion chemotherapy (see narratives of all 3 subjects in 6.1.12.3 Deaths). Of 11 subjects with ongoing neurologic toxicity, 7 had events ongoing at time of death from other causes while 4 subjects had ongoing events at data cutoff (1 of 4 subjects was lost to follow up). Of 7 subjects with ongoing NT at death, 6 had encephalopathy ongoing at death. Other neurologic events ongoing at death included delirium in 2 subjects, tremor in 2 subjects and aphasia in 1 subject. Of the 4 subjects with ongoing NT at data cutoff or last follow up, 3 had tremor and 1 had encephalopathy.

Table 33. Neurologic Toxicity Grade

Worst Neurologic Toxicity Grade	Subjects N (%)
Neurologic Toxicity Any Grade	95 (35%)
Grade 1	36 (13%)
Grade 2	28 (10%)
Grade 3	22 (8%)
Grade 4	6 (2.2%)
Grade 5	3 (1.1%)

Source: FDA Analysis of ADAE Dataset

The most common NTs include encephalopathy in 24% (65/268), tremor in 14% (37/268), aphasia in 9% (25/268), headache in 7% (18/268), delirium in 7% (20/268), dizziness in 6% (16/268) and ataxia in 6% (15/268) of subjects respectively. Cerebellar syndrome was reported in 3 subjects while 1 subject had cerebral edema that resolved.

All subjects with NT had neurologic events start within 8 weeks of JCAR017 infusion. The median time to onset of first event was 8 days (range 1 to 46 days). Median time to onset of maximum NT grade was 10 days (range 1 to 71 days). Neurologic toxicities resolved in 81 of 95 subjects (85%) with a median duration of 12 days (range 1 to 87 days). Median duration of NT in all subjects including those with fatal events and NT ongoing at death or data cutoff was 15 days (range 1 to 785 days). Please see Table 37 for details.

Table 34. Neurologic Events in 268 subjects in study 017001

Characteristic	Grade 1-5 N (%)	Grade 3-4 N (%)
Total number of subjects with NT	**95 (35%)**	**28 (10%)**
Encephalopathy*	65 (24%)	21 (8%)
Tremor*	37 (14%)	0
Aphasia*	25 (9%)	5 (1.9%)
Delirium*	20 (7%)	5 (1.9%)
Headache*	18 (7%)	2 (0.7%)
Dizziness*	16 (6%)	2 (0.7%)
Ataxia*	15 (6%)	1 (0.4%)
Paresis*	3 (1.1%)	1 (0.4%)
Cerebellar syndrome	3 (1.1%)	0
Motor Dysfunction*	3 (1.1%)	0
Depression*	3 (1.1%)	0
Vision blurred	2 (0.7%)	0
Seizure*	3 (1.1%)	3 (1.1%)
Brain Edema	1 (0.4%)	1 (0.4%)
Blindness*	2 (0.7%)	1 (0.4%)
Dysphagia	1 (0.4%)	1 (0.4%)
Urinary incontinence	2 (0.7%)	0
Visual field defect*	2 (0.7%)	0
Neuropathy peripheral*	1 (0.4%)	0
Nystagmus	1 (0.4%)	0
Depersonalization/derealization disorder	1 (0.4%)	0
Mydriasis	1 (0.4%)	0
Asthenia	1 (0.4%)	0
Trismus	1 (0.4%)	0
Deafness*	1 (0.4%)	0
Tinnitus	1 (0.4%)	0
Dysphonia	1 (0.4%)	0
Parosmia	1 (0.4%)	0
Social avoidant behavior	1 (0.4%)	0
Anal incontinence	1 (0.4%)	0

NT: Neurologic Toxicity; multiple events could have contributed to NT in subjects
**GT: grouped term; See APPENDIX A for Preferred terms and Grouped Terms used*
Source: adae.xpt, adsl.xpt

Table 35. Neurologic Toxicity in Different Dose Cohorts in study 017001

JCAR017 Dose Cohort	Number of Subjects	NT Grade 1-5 N (%)	NT Grade 3-4 N (%)
DL1S	45	12 (27)	6 (13)
DL2S	176	64 (36)	18 (10)
DL3S	41	18 (44)	3 (7)
DL1D	5	1 (20)	1 (20)
DL2D	1	0	0

Source: FDA analysis adae.xpt, adsl.xpt. Abbreviation: NT: neurologic toxicity; DL1S: dose level 1 single; DL2S: dose level 2 single; DL3S: dose level 3 single; DL1D; dose level 1, two-dose; DL2D: dose level 2, two-dose

Table 36. Time to Onset, Time to Resolution and Duration of NT in study 017001

JCAR017 Dose Cohort	Median time to onset in days (range) N=95	Median time to resolution in days (range) N=81	Median duration of NT in days (range) N=95
Overall	8 (1-46)	12 (1-87)	15 (1-801)
DL1S	8.5 (1-18)	8.5 (2-47)	11 (2-55)
DL2S	8.5 (1-46)	15 (1-84)	16 (1-801)
Dl3S	6.5 (1-18)	6.5 (2-87)	16 (2-313)
DL1D	10 (10-10)	17 (17-17)	17 (17-17)
DL2D	NA	NA	NA

Source: FDA analysis adae.xpt, adsl.xpt

Abbreviations: DL1S: dose level 1 single; DL2S: dose level 2 single; DL3S: dose level 3 single; DL1D; dose level 1, two-dose; DL2D: dose level 2, two-dose

Neurologic toxicity and CRS

Seventy-eight subjects (82%) with NT had CRS. Neurologic toxicity started and/or ended before, during or after CRS onset and resolution. Neurologic toxicity overlapped with CRS in 57 subjects. The onset of NT was after onset of CRS in 30 subjects, before CRS onset in 13 subjects, same day as CRS onset in 7 subjects and same day as CRS resolution in 7 subjects. Three subjects had resolution of NT before CRS onset while 18 subjects experienced start of NT after CRS resolved.

Table 37. Unresolved/Ongoing neurological toxicity events at death or data cutoff

USUBJID	Preferred Term	FDA GT	CTCAE Grade	AE Start day	Death or data cutoff day	Duration in Days
(b) (6)	Mental status changes, encephalopathy	Delirium Encephalopathy	2 2	10	94**	85
	Delirium, agitation	Delirium	3	4	33**	30
	Tremor	Tremor	1	23	807*	785
	Tremor	Tremor	1	29	179*	151
	Encephalopathy	Encephalopathy	4	8	63**	56
	Lethargy, somnolence	Encephalopathy	3	30	45**	16
	Leukoencephalopathy	Encephalopathy	2	148	163*	16
	Encephalopathy	Encephalopathy	1	30	60**	31
	Tremor	Tremor	1	3	315*	313
	Encephalopathy	Encephalopathy	3	18	26**	9
	Tremor	Tremor	1	13	149*	137

*USUBJID unique subject identification number; all USUBJIDs listed in the table have a prefix of 017001(study identifier), CTCAE: Common Terminology Criteria for Adverse Events v 4.03, FDA GT = FDA grouped term, AE: adverse event; AE start day is 1st day of 1st event * Ongoing at the time of data cutoff ** Death*

Management of Neurologic Toxicity

Corticosteroids, antiepileptic medications and IL-6 agents were used in NT management (Table 38). Antiseizure medications were used as prophylaxis or treatment.

Table 38. Medications in Management of Neurologic Toxicity

Medication	DL1S (N=45) n (%)	DL2S (N=176) n (%)	DL3S (N=41) n (%)	DL1D (N=6) n (%)	Overall (N=268) n (%)
Corticosteroids	7 (15.6)	28 (15.9)	10 (24.4)	1 (16.7)	46 (17.2)
Antiseizure Prophylaxis	12 (26.7)	54 (30.7)	16 (39)	0	82 (30.6)
Antiseizure Treatment*	7 (15.6)	24 (13.6)	9 (22)	1 (16.7)	41 (15.3)
Tocilizumab	1 (2.2)	7 (4)	1 (2.4)	0	9 (3.4)
Tocilizumab and Corticosteroids	1 (2.2)	7 (4)	0	0	8 (3)

Source: Applicant analysis; response to information request #75
**May be an overestimate; see clinical reviewer comments below*

Concomitant Medications: See Tables 31 and 38 under CRS and NT Management. Please see details of immunoglobulin replacement therapy for hypogammaglobulinemia below.

Clinical reviewer's comments

- *Neurologic toxicity consisted of different neurologic and/or psychiatric manifestations with or without overlapping time courses. Duration of NT was calculated from time of onset of the first event until resolution of the last event. The Applicant calculated duration of NT using the same formula as the Agency.*

- *The clinical team grouped several AEs (AEDECOD terms in the dataset) under a single term (FDA Group term) as outlined in APPENDIX A whenever possible. Grouping was based terms used in other files and clinical judgement of the group term most likely to fit the AEDECOD term under consideration e.g. stupor and loss of consciousness were grouped under encephalopathy. The FDAs group and preferred terms did differ from the Applicant's which explains the difference in incidence of certain AEs. However, Applicant was provided with the FDA's list of group and preferred terms for the label.*

- *Applicant had identified 80 subjects with NT. We looked at subjects with nervous system disorders or psychiatric disorders system organ class (SOC) not flagged as having NT. We looked at symptoms from these 2 SOCs in relation to each other and to JCAR017 infusion, occurrence of CRS and lack of alternate explanation for symptoms. Based on timing, occurrence of multiple symptoms and no clear-cut alternate explanation for symptoms, we initially identified 33 subjects with possible NT. After review of detailed narratives and Applicant's explanation, we identified 17 additional subjects of the 33 with NT. Some subjects with isolated symptoms e.g. headache that could have been related to JCAR017 were nevertheless not adjudicated as having NT since symptoms like headache are non-specific. On the other hand, tremor even in isolation is a more specific albeit non-life-threatening symptom which we considered as related to JCAR017 in majority of the cases while appreciating the fact that tremor is not a symptom included in the recent 2019 ASTCT (American Society of Transplant and Cellular Therapy) ICANS (Immune*

effector Cell Associated Neurotoxicity Syndrome) consensus criteria. We removed 2 subjects with NT flagged by the Applicant-one subject clearly had progressive multifocal leukoencephalopathy (017001-(b) (6)); the other subject (017001-(b) (6) had neurologic symptoms from hypercalcemia of malignancy. Hence, a total of 95 subjects were deemed to have NT. Brief narratives of the 17 subjects with NT identified by the clinical reviewer are provided below.

Subject 017001-(b) (6) Grade 1 tremor days 19-59 deemed by investigator to be related to JCAR017 with no alternative explanation.

Subject 017001-(b) (6) Grade 1 tremor days 16-17, grade 1 dizziness days 15-32 which was deemed related to JCAR017 by investigator; no alternative explanation for symptoms

Subject 017001-(b) (6) Grade 1 bradyphrenia days 3-4 which was deemed by investigator to be related to JCAR017. Symptoms overlapped with CRS and no sedatives given during this time to explain symptom.

Subject 017001-(b) (6) Grade 1 tremor days 15-16 deemed to be related to JCAR017 by the investigator

Subject 017001-(b) (6) Grade 5 encephalopathy; see 6.1.12.3 Deaths

Subject 017001-(b) (6) Grade 1 confusion days 16-19, day 24; grade 2 lethargy days 17-17, grade 1 headache day 18 and grade 1 depression days 18-27. Subject had multiple symptoms with overlapping/sequential timeframe of occurrence. Opiate medications did not explain symptoms and subject was placed on Levetiracetam prophylaxis indicating that investigator thought these symptoms could be that of NT from JCAR017.

Subject 017001-(b) (6) Grade 5 leukoencephalopathy thought to be more likely due to Fludarabine induced toxicity although contribution from JCAR017 cannot be completely ruled out. Symptoms characterized by blindness, asthenia, gait disturbances and periventricular white matter changes on MRI. Creatinine was 2.19 mg/dl prior to lymphodepletion, and it does not appear that Fludarabine dose was modified for renal insufficiency. See narrative in Section 6.1.12.3 Deaths*.*

Subject 017001-(b) (6) Grade 1 irritability on day 7 followed by grade 1 tremor days 8-22. Symptoms consistent with NT seen with CAR-T products and subject had CRS as well.

Subject 017001-(b) (6) Grade 1 agitation day 5 consistent with NT with CAR-T therapy

Subject 017001-(b) (6) Grade 1 tremor and headache days 11-12 deemed to be consistent with NT due to CAR-T therapy

Subject 017001-(b) (6) Grade 1 dizziness days 10-11, grade 2 balance disorder days 10-13 and grade 1 somnolence days 12-13. Multiple symptoms consistent with NT with no opiates given at time of symptoms to explain them

Subject 017001-(b) (6) *Grade 1 confusion days 10-13 with concurrent CRS. Symptoms deemed consistent with NT*

Subject 017001-(b) (6) *Grade 1 somnolence days 2-3 that occurred before CRS*

Subject 017001-(b) (6) *Grade 1 tremor starting day 3 that remained ongoing; grade 1 cognitive disorder days 7-8. Subject had CRS after onset of tremors and cognitive disorder followed resolution of CRS*

Subject 017001-(b) (6) *Grade 2 confusional state days 1-4, encephalopathy grade 1 days 4-5 and 8-18, grade 2 days 6-8 and 3 day 18 that remained ongoing at death. Had waxing and waning symptoms consistent with NT; hypoxia did not explain neurological symptoms. Had grade 4 CRS as well.*

Subject 017001-(b) (6) *Grade 1 mental status changes days 1-6 that occurred before CRS onset. Degree of anemia and hypotension do not explain symptoms.*

Subject 017001-(b) (6) *Grade 1 tremor days 18-78. Applicant cited other medications as cause, but tremor resolved despite these medications being continued. Hence, tremor deemed related to JCAR017.*

- *We identified 3 deaths from NT (see 6.1.12.3 Deaths)- all 3 from encephalopathy with 1 subject (017001-*(b) (6) *) deemed likely to have Fludarabine induced leukoencephalopathy. One another subject (017001-*(b) (6) *) was deemed to have Fludarabine induced leukoencephalopathy starting day 30 with symptoms (visual difficulties, asthenia, urinary incontinence, falls, memory issues, apraxia) reportedly ongoing but improving over time. Both subjects with likely Fludarabine induced leukoencephalopathy had renal failure at baseline which is a risk factor for Fludarabine toxicity. One subject received the full dose of Fludarabine (017001-*(b) (6) *while the other subject had Fludarabine dose reduced by 20%. We decided to include these subjects in the analysis of neurologic toxicity since toxicity of the entire investigational protocol including lymphodepleting chemotherapy is analyzed and not just JCAR017 infusion.*

- *One subject (017001-*(b) (6) *had focal brain edema that resolved.*

- *For 17 subjects already flagged by the Applicant as having NT, we flagged additional symptoms as being part of the NT or changed the grade based on review of the narratives. Additional symptoms were flagged based on occurrence with other symptoms deemed to be neurologic toxicity, no alternative explanation and timing related to CAR-T infusion and/or occurrence of CRS. Brief description of these changes is provided below.*

  Subject 017001(b) (6) *Grade of NT changed from 4 to 5; see narrative in 6.1.12.3 Deaths.*

  Subject 017001-(b) (6) *Grade 2 irritability days 11-51 flagged as NT; deemed to be related to JCAR017 by investigator. Already had amnesia reported as symptom of NT.*

Subject 017001-(b) (6) *Grade 1 tremor days 17-30 and grade 1 headaches days 13-30 flagged as NT. Symptoms overlapped with CRS and no alternative explanation*

Subject 017001-(b) (6) *Grade 1 visual field defect days 2-3, grade 1 headache days 4-5 and then days 12-14 flagged as additional symptoms. These symptoms preceded CRS following which subject had other symptoms of NT like aphasia.*

Subject 017001-(b) (6) *Grade 1 headache days 5-6 and dizziness days 8-16 added to other more specific symptoms of NT like aphasia since they occurred in the same time frame.*

Subject 017001-(b) (6) *Grade 1 headache days 29-36 flagged with other symptoms of NT like agitation, mental status changes around the same timeframe.*

Subject 017001-(b) (6) *Grade 3 agitation flagged as NT in subject with grade 3 encephalopathy days 8-19.*

Subject 017001-(b) (6) *Grade 1 tremor days 6-22 flagged as NT in subject already having confusional state during the same time frame.*

Subject 017001-(b) (6) *Grade 1 headache and mental impairment added to neurological symptoms in subject with other symptoms of neurologic toxicity like aphasia, seizures and encephalopathy. Toxicity grade changed to grade 4 from grade 3 given that status epilepticus is grade 4 toxicity.*

Subject 017001-(b) (6) *Grade 1 tremor day 6, grade 1 gait disturbance days 7-8 and motor dysfunction on day 10 flagged as NT in subject already flagged with lethargy as NT and having CRS during this time period.*

Subject 017001-(b) (6) *Please see description below under fludarabine induced leukoencephalopathy. Gait disturbance, leukoencephalopathy flagged as NT in subject with other symptoms of neurologic toxicity.*

Subject 017001-(b) (6) *Grade 1 dizziness days 15-22 and then on days 29-65 flagged as NT deemed to be related to JCAR017 by investigator*

Subject 017001-(b) (6) *Grade 1 dizziness days 19-22 added to dizziness occurring days 6-9 and identified as NT by the investigator*

Subject 017001-(b) (6) *Grade 1 dizziness days 1-3 and grade 1 headache days 1-2 added to other symptoms of NT flagged by the investigator*

Subject 017001-(b) (6) *Grade 1 dizziness day 10-13, grade 1 visual field defect day 12-13 and ongoing tremor starting day 13 flagged as additional symptoms of NT since they occurred in the same time frame as other symptoms flagged as NT by the investigator.*

Subject 017001-(b) (6) *Grade changed from 2 to 4 since per CTCAE v 4.03, even focal brain edema is grade 4 toxicity.*

- *Overall NT was higher in dose level 3 compared to dose levels 1 and 2 (see Table 35) but grade 3 or higher events were not more at a dose level 3 given fewer number of subjects with grade 3 or higher NT*

- *There is a discrepancy between the numbers of all grade and grade ≥ 3 encephalopathy between treatment emergent encephalopathy and that listed under neurologic toxicity. This is because treatment emergent encephalopathy includes encephalopathy from all causes e.g. sepsis, sedative medications etc. while that described under neurologic toxicity is encephalopathy attributed to KCAR017 or lymphodepletion chemotherapy.*

- *Forty seven of 95 subjects with NT (49%) received corticosteroids and/or tocilizumab. Corticosteroids alone was used in 38 subjects (38/95; 40%) with NT. Only 1 subject received tocilizumab alone which is in keeping with current management guidelines in that tocilizumab should be used in subjects with NT only with concurrent NT. Corticosteroids used for NT and/or CRS and NT included mainly dexamethasone and methylprednisolone*

- *Antiseizure medications used in study 017001 included levetiracetam, lacosamide, phenobarbital, phenytoin and fosphenytoin. Majority of the 95 subjects (82 of 95; 86%) received antiseizure prophylaxis. Antiseizure medications as treatment is likely an overestimate since if subjects were on antiseizure medications between start and end dates of NT, it was considered as treatment even if the intent may have been prophylaxis. Only 3 subjects of 268 had seizures.*

Infections

All grade infections including febrile neutropenia occurred in 45% (121/268) subjects with grade 3 or higher infections occurring in 19% (52/268) subjects. Table 39 details infections by broad pathogen class e.g. bacterial infections. Febrile neutropenia occurred in 24 subjects (9%). Sepsis occurred in 12 subjects of which 3 were fatal (see Section 6.1.12.3 Deaths)

Table 39. Infections by pathogen class in 268 DLBCL subjects in study 017001

Pathogen Class*	Any grade n (%)	Grade 3 or higher n (%)
Bacterial infection	35 (13)	15 (5)
Viral infection	27 (10)	4 (1.5)
Fungal infection	21 (8)	1 (0.4)
Unspecified	77 (29)	42 (16)

Source: FDA analysis of adae.xpt
** Includes group terms; see APPENDIX A for preferred terms included in specific group terms*

Table 40. Infection by select sites in 268 DLBCL subjects in study 017001

Site of Infection*	Any grade n (%)	Grade 3 or higher n (%)
Upper respiratory tract	34 (13)	2 (0.7)
Urinary tract	11 (4.1)	5 (1.9)
Pneumonia	22 (8)	12 (4.5)

Source: FDA analysis of adae.xpt
** Includes group terms; see APPENDIX A for preferred terms included in specific group terms*
Abbreviations: DLBCL: diffuse large B-cell lymphoma

Clinical Reviewer Comments

- *One subject with asymptomatic bacteruria was excluded from the analysis since this represents colonization and not true infection of the urinary tract. One AE of candiduria was similarly removed since this represents fungal colonization of the urinary tract; this subject however had other infections and is included in the analyses.*
- *Preferred terms under bacterial infections included conditions like appendicitis which are typically treated as bacterial infections.*
- *One subject with febrile neutropenia was incorrectly graded as grade 2. By CTCAE v 4.03, febrile neutropenia is at a minimum classified as grade 3.*
- *Notable infections included one case each of listeria meningitis, JC virus infection (progressive multifocal leukoencephalopathy-PML) and bronchopulmonary aspergillosis. Subject with PML died of the infection.*
- *Since infections were analyzed by pathogen and by site, subjects may have been included in both analyses. For calculation of infection by pathogen, the group term e.g. viral infection along with other terms where the pathogen was specified e.g. viral UTI was included in the analyses.*

Secondary Malignancies

Risk of insertional mutagenesis resulting in secondary malignancies is a concern with CAR-T therapy. Secondary malignancies were defined as newly diagnosed reports of cancer not representing relapse of the underlying disease for which the subject received study treatment. Five subjects (1.9%) had secondary malignancies reported in the treatment-emergent period of which 1 subject had peripheral T-cell lymphoma that was evaluated and deemed not to be a result of CAR-T therapy. Remainder had skin cancers and there was one case of endometrial adenocarcinoma. Ten of 247 subjects (4%) developed a secondary malignancy in the post-treatment emergent period. Five had hematologic malignancies of which 4 had MDS and 1 had acute myeloid leukemia. Six subjects (including one subject who also had MDS) developed solid tumors (n=4 with basal cell carcinoma, n=2 with cutaneous squamous cell carcinoma, n=1 appendiceal carcinoma). A single subject had 5 malignancies (MDS, 2 cutaneous basal cell cancer and 2 cutaneous squamous cell cancer).

Clinical Reviewer Comments

- *Subject 017001-*(b) (6) *had peripheral T-cell lymphoma (PTCL) diagnosed post JCAR017 therapy. Tumor sample was assayed for JCAR017 vector transgene levels using a non-validated assay which revealed transgene levels below that detected concurrently in peripheral blood. Results were deemed inconsistent with CAR-T cell associated clonal proliferation. An insertional site analysis did not show evidence of insertional mutagenesis.*

- *While reviewing BLA death narratives, clinical reviewer noted that subject 017001-*(b) (6) *developed MDS on day 70 following JCAR017 infusion and was stated to have 1 CAR transgene in the MDS sample. Hence, an IR was sent requesting additional data on this case and reports of all MDS cases to date. Please see Table 41 below. Based on Sponsor's response and discussion with CMC, this subject*

was deemed not to have CAR-t cell associated malignancy given low-level detection in a single cell. Insertional site analysis was not performed in this subject for the aforementioned reason.

Table 41. Myelodysplastic syndrome & Transgene testing in study 017001

USUBJID	AE onset day	Sample received at test lab	Sample adequate Y/N	JCAR017 RNA*scope in-situ hybridization* results
(b) (6)	490	Y	Y	Negative for CAR-T
	106	Y	Y	Negative for CAR-T
	174	Y	Y	Negative for CAR-T
	336	Y	Y	Negative for CAR-T
	70	Y	Y	1 CAR-T cell detected
	732	N	NA	Not done
	678	N	NA	Not done

Source: Applicant response to IR#18, Data cutoff March 12, 2020
USUBJID: Unique subject identifier; all have prefix of 017001 to indicate study number, Y/N: yes/no
AE: adverse event, NA: not applicable; CAR-T: chimeric antigen receptor-T (cell)

- *All subjects with secondary malignancies were in the DL2S dose regimen cohort*

Prolonged Cytopenias

Prolonged cytopenias are defined as neutropenia, thrombocytopenia or anemia persisting present at day 29 following JCAR017 infusion. All grade cytopenias were present in 149 (56%) subjects. Grade 3 or higher cytopenias present at day 29 occurred in 31% (84/268) of subjects. Grade 3 or higher thrombocytopenia, neutropenia and anemia occurred in 26%, 14% and 3% of subjects respectively.

Clinical Reviewer Comments

- *We requested Applicant to do the analysis based on the laboratory (ADLB) dataset rather than using the adverse event dataset (ADAE dataset) since this is more accurate. Day 29 cytopenias were not flagged in the datasets; hence we could not do the analysis. Parameters for blood or platelet transfusion in determining the acceptability of hemoglobin or platelet counts for analysis were specified by the Applicant and were deemed acceptable*
- *Prolonged neutropenia and thrombocytopenia increase risk of infection and bleeding respectively*

Hypogammaglobulinemia

Hypogammaglobulinemia as an adverse event was reported in 37 subjects (14%) with no grade 3 or higher events reported. Laboratory based hypogammaglobulinemia (defined as IgG of < 500 mg/dl) occurred in 56 subjects (21%). Hypogammaglobulinemia, either as an adverse reaction or on the basis of an IgG < 500mg/dl, was reported in 32% (85/268). .Intravenous immune globulin (IVIG) therapy was not mandated in the protocol for a defined IgG cutoff level and was left up to the clinician's discretion.

Clinical Reviewer Comment

- *The PI reflects a combination of adverse event and laboratory based hypogammglobulinemia*
- *Per Applicant, the vast majority of subjects with hypogammaglobulinemia did not receive IVIG and presumably did fine, we agree that IVIG replacement can be left to institutional clinical practice and judgement. The analysis of IVIG replacement therapy by the Applicant included all events of hypogammaglobulinemia based on laboratory analyses during the study and was not restricted to the treatment emergent period.*
- *There is no analysis on the correlation between hypogammaglobulinemia and infections*

Tumor Lysis syndrome
Tumor lysis syndrome was reported in 2 subjects (0.7%) in the study. Both events were grade 3.

Infusion Related Reaction
Infusion related reaction occurred in 3 subjects (1.1%) on the study. No event was grade 3 or higher and occurred on the same day as JCAR017 infusion.

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)
No events were reported on the trial.

Clinical Reviewer Comment

- *Although no cases of HLH/MAS were reported in study 017001, review of safety data from the ISS revealed a case of HLH.MAS. Additionally, HLH/MAS has been well described as a complication of CAR-T therapy. HLH/MAS has overlapping features with CRS and may be considered by some as severe CRS. Hence, we recommend that Applicant keep HLH/MAS as a sign/symptom of CRS in the PI so that clinicians are aware of this possibility in subjects who receive JCAR017*

Hospitalization

Hospitalization data was collected from 1st day of LDC through end of study. Seven of 268 subjects were never hospitalized. Median time for initial hospitalization following JCAR017 administration was 11 days (range 2 to 88 days). Nineteen of 268 subjects (7%) required ICU admission with a median number of ICU days of 7 (range 1-56 days). Hospitalization data on subjects who received JCAR017 in the inpatient setting (243/268; 91%) closely mirrors that of the hospitalization data for all subjects. For hospitalizations recorded through end of study, median total days of hospitalization was 17 days (range 2-116 days) with 12% ICU admissions (32/268 subjects) and median ICU stay of 7 days (range 1-56 days).

6.1.12.6 Clinical Test Results

Table 42 summarizes common (occurring in 10% or more of subjects) treatment-emergent laboratory abnormalities in the safety population.

Table 42. Laboratory based abnormalities in ≥ 10% subjects*

Laboratory Based Abnormality	All grades n(%)	Grade 3-4 n(%)
Hematology		
Neutropenia	201 (75)	190 (71)
Thrombocytopenia	177 (68)	104 (39)
Anemia	129 (45)	58 (22)
Chemistry		
Hypertriglyceridemia	156 (58)	15 (6)
Hyponatremia	89 (33)	14 (5)
Hypomagnesemia	70 (26)	0
Hypophosphatemia	89 (33)	36 (13)
Hypoalbuminemia	91 (34)	6 (2.2)
Serum Creatinine increased	40 (15)	1 (0.4)
Serum ALT increased	55 (21)	2 (0.7)
Hypokalemia	62 (23)	6 (2.2)
Serum Alkaline Phosphatase increased	52 (20)	4 (1.5)
Serum Bilirubin increased	25 (9)	4 (1.5)
Serum AST increased	58 (22)	2 (0.7)
Hypercalcemia	15 (6)	0
Hypoglycemia	10 (3.7)	0
Hypermagnesemia	17 (6)	1 (0.4)
Hypocalcemia	24 (9)	1 (0.4)
Coagulation		
Hypofibrinogenemia[$]	234 (89)	39 (15)
Blood INR increased	116 (64)	2 (1.1)
Blood aPTT increased	90 (34)	10 (3.7)

Source: FDA analysis adlb.xpt, adsl.xpt
**The laboratory-based abnormality terms used do not reflect grouped terms but reflect common medical terminology for abnormal laboratory findings e.g. hemoglobin decreased is anemia*
Abbreviations: ALT: alanine aminotransferase; ASTL aspartate aminotransferase; INR; international normalized ratio; aPTT activated partial thromboplastin time $Denominator 263 instead of 268

Clinical Reviewer Comments

- *Laboratory data (ADLB dataset) was used to generate incidence of laboratory-based AEs since this is more accurate as opposed to using the adverse event dataset (ADAE dataset).*
- *A "lab-shift" analysis was carried out wherein baseline laboratory abnormalities that worsened following treatment were recognized i.e. shift of a laboratory grade from a lower to higher grade.*
- *Cytopenias of all grades were the most common laboratory abnormalities as expected and reflect toxicity of the entire investigational protocol including lymphodepleting chemotherapy.*
- *Although hypophosphatemia was the 4th most common overall abnormal chemistry laboratory value, it was the most common grade 3-4 chemistry laboratory abnormality.*
- *Hypofibrinogenemia was the most common overall and grade 3-4 coagulation abnormality but overt bleeding resulting from coagulation abnormalities e.g. disseminated intravascular coagulation was not reported in the trial. Grade 3 and*

higher hemorrhage and gastrointestinal hemorrhage ((see preferred terms under these grouped terms in APPENDIX A) were noted in 5 (1.9%) and 4 (1.5%) of subjects respectively.

6.1.12.7 Dropouts and/or Discontinuations

Four hundred and twenty-four subjects were screened of which 338 were successfully screened for the DLBCL cohort. Three hundred and thirty-six underwent leukapheresis; six other subjects underwent leukapheresis but were retrospectively deemed to be screen failures (so total of 342 leukapheresed subjects). Two hundred and sixty-eight received conforming JCAR017 product. Cause for not receiving JCAR017 product in 74 subjects include 27 subjects with manufacturing failure (24 subjects with non-conforming product), failure to meet eligibility criteria for study (n=3) or JCAR017 infusion (n=7), withdrawal of consent (n=2), death (n=33) mainly due to progressive disease, disease related complications (n=6) and other (n=2).

Clinical Reviewer Comment

- *The numbers in the disposition in the section above are drawn based on the review of the clinical study report and from the 268 subjects for safety at the primary data cutoff of April 12, 2019. The numbers in the PI reflect the analyses in the population from which the efficacy analyses were conducted and based on IRs sent by the efficacy reviewer. The disposition of subjects in study 017001, especially as it relates to manufacturing failure, is accurately reflected in the PI and the efficacy reviewer's analyses as opposed to the safety reviewer's delineation of data from the clinical study report in section 6.1.12.7 above*.

6.1.13 Study Summary and Conclusions

Safety

Of the 268 subjects in the safety evaluable set, grade or higher toxicities for the AEs of concern are as follows:

- CRS occurred 4%
- Neurologic toxicities 12%
- Febrile neutropenia occurred in 9%
- Prolonged cytopenias (present ≥ day 29) occurred in 31%
- Infections occurred in 19% (includes febrile neutropenia)

The 30-day fatal AE rate was 1.7% and overall fatal AE rate was 4%. Cytokine release syndrome, neurologic toxicity including that from the lymphodepleting chemotherapy, sepsis, pulmonary hemorrhage, cardiomyopathy, JC virus infection and MDS were the cause of fatal AEs. The toxicity profile of JCAR017 is similar to other products in its drug class.

During TRANSCEND (study 017001), life-threatening and fatal adverse reactions caused by JCAR017 were mitigated by mandated site and investigator training, careful site selection and monitoring, instructions for early detection and management of the most serious complications, and close monitoring following JCAR017 infusion. Hospitalization was not mandated but 91% of subjects received treatment in the inpatient setting. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and neurotoxicity, and a REMS. The clinical review team determined, in consultation with OBE and CDER DRISK, that a REMS with ETASU is the appropriate approach. The

focus of the REMS with ETASU are site preparation, patient education, and risk mitigation strategies, with emphasis on early recognition and treatment of CRS and neurotoxicity.

Long-term safety after treatment with JCAR017 especially for secondary malignancies remains a concern. None of the secondary malignancies during this trail at time of primary data cutoff were attributed to the study product but concern for insertional mutagenesis and secondary malignancies remain. Due to the lack of long-term safety data in the BLA, additional post-marketing registry has been mandated.

7. INTEGRATED OVERVIEW OF EFFICACY

Only one study was evaluated in this BLA review and therefore no integrated analysis of efficacy was performed.

7.1 Indication #1

7.1.1 Methods of Integration

N/A

7.1.2 Demographics and Baseline Characteristics

N/A

7.1.3 Subject Disposition

N/A

7.1.4 Analysis of Primary Endpoint(s)

N/A

7.1.5 Analysis of Secondary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

N/A

7.1.8 Persistence of Efficacy

N/A

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

The efficacy of JCAR017 is based on CR rate and DOR in a multicenter, open label, single arm clinical trial in adults with relapsed or refractory or transformed DLBCL after two lines of systemic regimens. Of 344 subjects, 269 subjects were treated by infusion with JCAR017 at the dose range of 44×10^6 to 156×10^6 CAR+ T cells. The dose range of 50×10^6 to 110×10^6 CAR+ T cells is the recommended regimen of dose for this BLA approval. 256 of the 269 treated subjects in the DLBCL cohort were efficacy-evaluable and therefore constituted the primary evidence of efficacy for the product. The majority of subjects (75%) received the study drug at the recommended dose schedule. By independent review committee (IRC)-FDA assessment, ORR was 73.4% (95% CI: 65.5%,

76.9%). The lower limit of the 95% exact Clopper-Pearson confidence interval was greater than the pre-specified null hypothesis rate of 40%. The complete response (CR) was 54% according to Lugano criteria. Of the 141 subjects who achieved an objective response, 57.1% maintained response for at least 6 months and 52.8% maintained a response for at least 12 months. The durability of response following PR was transient (mDOR of 2 months)

8. INTEGRATED OVERVIEW OF SAFETY

Only one study was evaluated in this BLA review for safety and no detailed integrated analysis of safety was performed. Safety data from 43 additional subjects included in the ISS from trials BCM001and BCM002 were scanned to see if there were any new concerns but no new safety signal was identified.

8.1 Safety Assessment Methods
N/A

8.2 Safety Database
N/A

8.2.1 Studies/Clinical Trials Used to Evaluate Safety
N/A

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations
N/A

8.2.3 Categorization of Adverse Events
N/A

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials
N/A

8.4 Safety Results

8.4.1 Deaths
N/A

8.4.2 Nonfatal Serious Adverse Events
N/A

8.4.3 Study Dropouts/Discontinuations
N/A

8.4.4 Common Adverse Events
N/A

8.4.5 Clinical Test Results
N/A

8.4.6 Systemic Adverse Events
N/A

8.4.7 Local Reactogenicity
N/A

8.4.8 Adverse Events of Special Interest
N/A

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events
N/A
8.5.3 Product-Demographic Interactions
N/A
8.5.4 Product-Disease Interactions
N/A
8.5.5 Product-Product Interactions
N/A
8.5.6 Human Carcinogenicity
N/A
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
N/A
8.5.8 Immunogenicity (Safety)
N/A
8.5.9 Person-to-Person Transmission, Shedding
N/A

8.6 Safety Conclusions

As above.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No animal studies of reproduction or developmental toxicity have been performed, and JCAR017 has not been studied in pregnant women.

Clinical reviewer comment
Effective contraception was required for clinical trial participation of JCAR017. For information regarding the need for contraceptive use among patients treated with cyclophosphamide and fludarabine lymphodepleting conditioning chemotherapy, please see the respective agents' prescribing information

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

There are no pediatric data in the intended population. The application does not trigger PREA, as lisocabtagene maraleucel (JCAR017) is a new molecular entity (NME) with orphan designation

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

Of the 268 subjects, 111 (41%) were 65 years of age or older and 27(10%) were 75 years of age or older. There were no relevant clinical differences that occurred in the safety or effectiveness of those older than 65 years compared to younger patients.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Adverse Events in Subjects with Secondary CNS lymphoma

Seven of 268 subjects (2.6%) had secondary CNS lymphoma at time of first JCAR017 infusion. Overall rate of TEAE was similar between those with secondary CNS lymphoma and those without (n=261) such involvement but rate of grade 3 TEAEs was higher in those with secondary CNS lymphoma (100%, 7/7 vs 78.5%, 205/261). No differences in AESI were noted especially as regards to NT. Grade 3 NT was noted in 2 subjects (depressed level of consciousness, dysphagia in subject 017001-(b) (6) and encephalopathy in 017001-(b) (6)). Review of narratives shows that in subject 017001-(b) (6) NT resolved, and subject had CR at day 30 following JCAR017 therapy. This subject had grade 2 CRS and subsequently died of progressive disease on day 232. Subject 017001-(b) (6) died of PML; lesion attributed to secondary CNS lymphoma could have been PML. We adjudicated that this subject did not have NT given PML diagnosis within 4 days of JCAR017 infusion.

Adverse Events in Subjects who Received Non-Conforming Product (NCP)

Twenty-four subjects were treated with nonconforming product. Nine subjects received CD8+ component only, 3 subjects received CD4+ component only and 12 received both components but product was deemed non-conforming due to potency (n=5), purity (n=1), sterility (n=1) and viability (n=5) issues. Overall frequency for grade 3 and higher TEAEs and AESI is similar to those who received conforming JCAR017. One subject had grade 5 mucormycosis on day 4. One subject who received only the CD8+ component had grade 5 recurrent squamous cell cancer on day 141. CRS was reported in 7 of 24 subjects (29%) with 1 subject having Grade 3/4 CRS. NT was reported in 3 of 24 subjects (12.5%) with 1 subject having grade 3 NT that was ongoing at death from disease progression on day 33.

Adverse Events in Retreated Subjects

Retreatment was defined as JCAR017 administration for progressive disease following CR as BOR after 1st JCAR017 administration. Fifteen subjects were retreated; 9 at DL2S, 5 at DL1S and 1 at DL3S. Majority (14/15, 93%) had AEs following retreatment with 80% (12/15). having grade 3-4 AEs. One subject had a grade 5 AE of “unknown” cause. The most frequent AEs following retreatment were cytopenias (anemia and neutropenia in 53% each, 8/15), pyrexia, nausea and CRS (each in 33%; 5/15). 1 subject had grade 3 CRS and 1 subject had CRS reported as ongoing at death.

Clinical Reviewer Comment

- *We had considered mentioning secondary CNS lymphoma specifically in the indication statement but given paucity of efficacy data and the use of CNS targeted bridging therapies without assessment of CNS disease status prior to LDC, the contribution of the investigational product in the observed CRs remain unclear.*

Safety data is limited but does the limited data provides information as to the feasibility from a safety standpoint of administering CNS targeted bridging therapy with the investigational product without increased risk of CNS toxicity.

10. CONCLUSIONS

Efficacy

The efficacy of JCAR017 is based on CR and DOR in a multicenter, open label, single arm clinical trial in adults with relapsed or refractory or transformed DLBCL after two lines of systemic regimens. The majority of subjects (75%) received the study drug at the recommended dose schedule. By independent review committee (IRC)-FDA assessment, ORR was 73.4% (95% CI: 65.5%, 76.9%). The lower limit of the 95% exact Clopper-Pearson confidence interval was greater than the pre-specified null hypothesis rate of 40%. The complete response (CR) was 54% according to Lugano criteria. Of the 141 subjects who achieved an objective response, 57.1% maintained response for at least 6 months and 52.8% maintained a response for at least 12 months. The basis of FDA's conclusion of substantial evidence of effectiveness is the magnitude of benefit primarily driven by durable complete response rate.

Safety

Severe CRS and neurotoxicity associated with JCAR017 therapy are serious and life-threatening and require supportive measures. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. In addition, there is the potential for insertional mutagenesis and resultant secondary malignancies. To enhance safety, the following measures should be followed:

1. The product label will allow for a boxed warning, and the warnings and precautions will convey a treatment algorithm for CRS and NT
2. REMS with ETASU to assure the safe use of JCAR017
3. PMR study that is a requirement to follow recipients of the commercial product for short term and long-term toxicity

In summary, Study 017001 represents an adequate and well controlled study that provided substantial evidence of effectiveness and safety.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The following table summarizes the risk/benefit considerations for BREYANZI 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.

Table 43. Risk benefit considerations in BREYANZI approval

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Aggressive B-cell NHLs are fatal if not cured. In DLBCL that is refractory or that relapses within 1 year after auto SCT, salvage regimens produce ORRs of 20-30%, with <15% CR and an estimated median OS of 6 months.	There is a need for effective and safe salvage therapies for relapsed or refractory, aggressive B-cell NHL
Unmet Medical Need	Patients with relapsed or refractory, aggressive B-cell NHL have unmet medical needs.	Patients with relapsed or refractory, aggressive B-cell NHL have unmet medical needs.
Clinical Benefit	• In this single arm multicenter study for patients with relapsed/refractory B Cell NHL, lymphodepleting chemotherapy followed by a dose of BREYANZI produced: • CR was 54.2% according to Lugano criteria, with a median DOR of 16.7 months • ORR, by independent review committee (IRC) assessment, was 73.4% (95% [CI] 66.6%, 79.5%)	Based on the CR rate and DOR, BREYANZ at the recommended dose range has clinically meaningful activity in relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy.
Risk	• Major AEs associated with BREYANZI were cytokine release syndrome, neurologic toxicities, prolonged cytopenias, infectious complications, and hypogammaglobulinemia.	All the evidence indicates that the risk of BREYANZI, while substantial, does not outweigh the benefit to adult patients with R/R B cell NHL.
Risk Management	• The most substantial risks of BREYANZI are CRS and neurologic toxicity. These were mitigated in the trail by careful site selection and training of investigators. • There are theoretical risks of secondary malignancy in this genetically modified immunotherapy based on the potential for replication competent retrovirus due to the retrovirus and insertional mutagenesis.	The risks associated with BREYANZI warrant boxed warnings, a REMS particularly for CRS and NT, and a long term follow up study for risk assessment of subsequent malignancy attributable to insertional mutagenesis

11.2 Risk-Benefit Summary and Assessment

The risks of lisocabtagene maraleucel (JCAR017) are associated with its mechanism of action. CRS and neurotoxicity can be life-threatening or fatal. Hypogammaglobulinemia can persist for months and requires monitoring and intervention. However, the risks may be managed with appropriate risk mitigation strategies in place.
JCAR017 is associated with a favorable risk/benefit balance for the recommended indication. A summary of the key efficacy and safety results is provided in Section 1.

11.3 Discussion of Regulatory Options

The safety profile of JCAR017 warrants a REMS with ETASU. In the IND phase, the applicant selected sites for expertise, conducted site training, and had close medical monitoring to assure that the unique adverse events were treated appropriately, and that patients and medical staff were educated on the risks, particularly of CRS and neurotoxicity. There are additional long-term safety concerns due to the use of a lentiviral vector. We have asked the applicant to comply with an observational PMR study for short- and long-term toxicities. Additionally, the label will be inclusive of the risks and risk mitigation strategies for CRS and neurotoxicity, including a requirement to monitor patients at the certified healthcare facility frequently following infusion of JCAR017.

11.4 Recommendations on Regulator

The review team recommends regular approval for JCAR017 for the treatment of adult patients with relapsed or refractory DLBCL after at least 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.
Although two other similar agents are indicated for this population based on CR and DoR, JCAR017 has demonstrated a greater magnitude and durability of CR rate with an acceptable safety profile.

11.5 Labeling Review and Recommendations

The key labeling negotiations included:
Indication:
Dosing and Administration:
- addition of dose range (50-110 CAR T cells) and removal of target dosing to facilitate a dose range supported by efficacy.
Safety:
- modifications to the warnings and precautions section
- clarification of subjects in the safety population (n=268)
Efficacy:
-clarification of efficacy evaluable population (n=256) and subjects who received BREYANZI within the dose range
- efficacy for subjects in recommended dose range
-deletion of median DOR follow up
-censor marks for median DOR

The final constitution of the product is complex given the separate vialing for CD4+ and CD8+ CAR T cells which require calculation of volumes for each cell component. Thus, the product will be dispensed with worksheets for calculation of volumes of each cell component for reconstitution of the product. Given the complexity of administration, it is unclear as to whether such reconstitutions should occur in cell processing laboratories and in the event that such facilities are not available at stand-alone infusions centers whether personnel should be trained to avoid medications errors. These issues were raised with the CMC review team. In addition, logistics related to receiving the products at stand-alone infusion centers where 24 hour capability to receive the shipped products and store under the required conditions may be limited and these issues were discussed with CMC. The review team recommends that the CMC team examine the practice of shipping to stand-alone infusion centers to understand the feasibility of the issues related to logistics and reconstitution of the product.

Reviewer Comment:
The labeling negotiations with the Applicant are ongoing at the time of completion of this review.

11.6 Recommendations on Postmarketing Actions

The Applicant is planning to conduct a post-marketing registry study which we will consider a PMR. This study is observational and focuses on short-term toxicity, documenting adverse events, and long-term follow-up for evaluation of secondary malignancies. The plan is to enroll approximately 1000 patients and follow each patient for 15 years.
The Applicant submitted a REMS that consisted of a communication plan and medication guide. We determined in consultation with the OBE and CDER DRISK that a REMS with ETASU is the most appropriate approach. The focus of the REMS ETASU is site preparation, patient education, and assessment of risk mitigation strategies on the recognition and treatment of CRS and neurotoxicity.
The REMS ETASU should be reviewed, approved, and implemented by the Applicant at participating treatment sites prior to the distribution of lisocabtagene maraleucel to the site. See Section 4.6 Pharmacovigilance for specific details of the REMS ETASU.

APPENDIX A

FDA grouped and preferred terms used in review of BLA 125714 is presented in table format below.

Grouped Term	Preferred terms
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
Aphasia	aphasia, disorganised speech, dysarthria, dysphemia, speech disorder, slow speech
Ataxia	ataxia, balance disorder, coordination abnormal, dysmetria, dyskinesia, gait

Grouped Term	Preferred terms
	disturbance, hand-eye coordination impaired
Bacterial infection	appendicitis, cellulitis, clostridium difficile infection, clostridium difficile colitis, diverticulitis, enterococcal infection, Gardnerella infection, Haemophilus infection, meningitis listeria, peritonitis, salmonellosis, skin infection, staphylococcal infection, tooth infection
Blindness	blindness, blindness unilateral
Bradycardia	bradycardia, sinus bradycardia
Cardiac Arrhythmias	arrhythmia, atrial fibrillation, atrioventricular block complete, atrioventricular block second degree, extrasystoles, supraventricular tachycardia, ventricular tachycardia
Cardiac failure	cardiomyopathy
Chest pain	chest pain, chest discomfort, angina pectoris
Coagulopathy	coagulopathy, international normalised ratio increased
Conjunctivitis	conjunctivitis, conjunctivitis bacterial
Cough	cough, productive cough, upper-airway cough syndrome
Cytomegalovirus infection	cytomegalovirus infection, cytomegalovirus viraemia
Deafness	deafness, deafness neurosensory, deafness unilateral
Delirium	agitation, delirium, delusion, disorientation, hallucination; hallucination, visual; irritability, restlessness

Grouped Term	Preferred terms
Depression	anhedonia, depression, decreased interest, depressed mood, flat affect, suicidal ideation
Dizziness	dizziness, presyncope, syncope, vertigo
Dyspnea	acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure
Ecchymosis	ecchymosis, catheter site bruise, contusion, eye contusion
Edema	fluid overload, fluid retention, generalised oedema, hypervolaemia, oedema, oedema peripheral, peripheral swelling, pulmonary congestion, pulmonary oedema, swelling
Encephalopathy	amnesia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, incoherent, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, somnolence
Fatigue	asthenia, fatigue, malaise
Fungal infection	candida infection, oral candidiasis, systemic candida, tinea pedis, vulvovaginal mycotic infection
Gastroenteritis	enterovirus infection, gastrointestinal viral infection
Gastrointestinal hemorrhage	gastric ulcer haemorrhage, gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage, melaena

Grouped Term	Preferred terms
Headache	headache, head discomfort, migraine, sinus headache
Hemorrhage	catheter site haemorrhage, conjunctival haemorrhage, epistaxis, intracranial, haemorrhage, haematoma, haematuria, pulmonary haemorrhage, retinal haemorrhage, vaginal haemorrhage
Herpes viral infections	herpes simplex, herpes zoster, human herpesvirus 6 infection
Hyperammonemia	hyperammonaemia, ammonia increased
Hyperbilirubinemia	blood bilirubin increased, hyperbilirubinaemia
Hyperglycemia	hyperglycaemia, blood glucose increased
Hyperphosphatemia	blood phosphorus increased
Hypofibrinogenemia	hypofibrinogenaemia, blood fibrinogen decreased
Hypotension	hypotension, orthostatic hypotension
Hypoxia	hypoxia, oxygen saturation decreased
Lymphopenia	lymphopenia, lymphocyte count decreased
Motor dysfunction	muscle spasms, muscular weakness, eyelid ptosis, motor dysfunction, myoclonus, muscle rigidity, muscle spasticity, muscle tightness, muscle twitching
Musculoskeletal pain	musculoskeletal pain, musculoskeletal discomfort, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia,

Grouped Term	Preferred terms
	back pain, bone pain, myalgia, neck pain, pain in extremity, spinal pain
Neuropathy peripheral	neuropathy peripheral, paraesthesia, hypoaesthesia, hyperaesthesia, peripheral sensory neuropathy, sciatica, neuralgia, sensory loss, meralgia paraesthetica
Oral Pain	oropharyngeal pain
Pain	axillary pain, breast pain, catheter site pain, ear pain, eye pain, facial pain, flank pain, gastrointestinal pain, groin pain, lymph node pain, non-cardiac chest pain, pain, pain in jaw, pelvic pain, pleuritic pain, procedural pain, stoma site pain, thyroid pain, tumour pain, urinary tract pain
Paresis	facial paralysis, hemiparesis, hemiplegia, diplegia, paresis, VIth nerve paralysis, peroneal nerve palsy, gaze palsy
Pericardial effusion	pericardial effusion, pericardial effusion malignant
Pneumonia	bronchopulmonary aspergillosis, lung infection, lung consolidation, pneumonia, pneumonia aspiration, organising pneumonia
Rash	erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, perineal rash, dermatitis acneiform
Reflexes abnormal	reflexes abnormal, hyporeflexia
Renal failure	acute kidney injury, blood creatinine increased, renal failure, renal injury, chronic kidney disease
Seizure	seizure, status epilepticus

Grouped Term	Preferred terms
Sepsis	sepsis, septic shock, bacterial sepsis, staphylococcal bacteraemia, enterococcal bacteraemia, streptococcal bacteraemia
Tachycardia	sinus tachycardia, tachycardia, heart rate increased
Thrombosis	cerebral venous thrombosis, deep vein thrombosis, vena cava thrombosis, venous thrombosis limb, embolism, pulmonary embolism, thrombosis
Transaminase elevation	alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased
Tremor	resting tremor, tremor, essential tremor
Upper respiratory tract infection	upper respiratory tract infection, sinusitis, nasopharyngitis, upper respiratory tract congestion, rhinovirus infection, rhinitis, pharyngitis
Urinary tract infection	escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, urinary tract infection viral
Viral infection	parainfluenzae virus infection, BK virus infection, corona virus infection, influenza, progressive multifocal leukoencephalopathy
Vision blurred	vision blurred, visual impairment
Xerosis	dry eye, dry skin, dry mouth