

**Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Sponsor: Juno Therapeutics, Inc., a Celgene Company

Product: BREYANZI (JCAR017; lisocabtagene maraleucel)

BLA Number: STN 125714/0

Proposed Indication: BREYANZI® is a CD-19 directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with relapsed or refractory large B-cell lymphoma after at least two prior therapies.

Submission Date: December 18, 2019

Action Due Date: November 16, 2020

1 Objective and Scope

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125714/0 based on the safety profile of Breyanzi® and to determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for Breyanzi (lisocabtagene maraleucel), should the product be approved.

2 Product Information

2.1 Product Description

Throughout this memorandum, italicized text is quoted verbatim from the source document.

BREYANZI (also referred to as JCAR017 during clinical development) is a CD19-directed genetically modified autologous cellular immunotherapy administered as a defined composition of CAR-positive viable T cells (consisting of CD8 and CD4 components). The CAR comprises an FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. In addition, BREYANZI includes a nonfunctional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR.*

BREYANZI is prepared from the patient's T cells, which are purified from the product of a standard leukapheresis procedure. The purified CD8-positive and CD4-positive T cells are separately activated and transduced with the replication incompetent lentiviral vector containing the anti-CD19 CAR transgene.

The BREYANZI formulation contains 75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1, 1% (v/v) of 25% albumin (human).

*Note: Breyanzi is used interchangeably with JCAR017 throughout this memorandum.

2.2 Proposed Product Indication and Dosing Regimen

The proposed product indication for Breyanzi is for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least two prior therapies.

Breyanzi is a cell suspension for intravenous (IV) infusion. Dosing is based on the number of chimeric antigen receptor (CAR)-positive viable T cells. *A single dose of Breyanzi contains a target of 100×10^6 CAR-positive viable T cells (consisting of CD8*

and CD4 components), with each component supplied separately in one or more single-dose vials.

2.3 Pertinent Regulatory History

Pertinent regulatory history is shown in Table 1.

Table 1: Pertinent Regulatory History

Date	Regulatory Action
May 29, 2015	IND 16506 submitted to FDA; became active on June 26, 2015; first subject treated on February 22, 2016
April 27, 2016	Orphan Drug Designation for diffuse large B-cell lymphoma (DLBCL) (Designation #15-5161)
December 16, 2016	Breakthrough Therapy designation for treatment of patients with R/R aggressive large B-cell non-Hodgkin lymphoma (NHL), including DLBCL, not otherwise specified (NOS) (de novo or transformed from indolent lymphoma), primary mediastinal B-cell lymphoma (PMBCL), or follicular lymphoma Grade 3B (FL3B)
September 7, 2017	Orphan Drug Designation for follicular lymphoma (Designation #17-6005)
October 20, 2017	Regenerative Medicine Advanced Therapy designation for treatment of patients with R/R aggressive large B-cell NHL, including DLBCL, NOS (de novo or transformed from indolent lymphoma), PMBCL, or FL3B
July 12, 2018	Orphan Drug Designation for PMBCL (Designation #18-6440)

3 Materials Reviewed

- Pharmacovigilance Plan, Version 1.0, September 30, 2019 (STN 125714/0.1, Module 1.16.1, received October 30, 2019)
- Draft Registry Protocol, JCAR017-DLBCL-001 (STN 125714/0.1, Module 1.16.1, dated September 10, 2019, received October 30, 2019)
- Draft Registry Statistical Analysis Plan, Version 0.4 (STN 125714/0.1, Module 1.16.1, dated September 10, 2019, received October 30, 2019)
- Long-term Follow-up (LTFU) Protocol for Subjects Treated with Gene-Modified T Cells (STN 125714/0.1, dated May 31, 2017, received October 30, 2019)
- Risk Evaluation and Mitigation Strategy (STN 125714/0.1, Module 1.16.2, received October 30, 2019)
- Clinical Overview (STN 125714/0.1, Module 2.5, received October 30, 2019)
- Clinical Safety (STN 125714/0.1, Module 2.7, received October 30, 2019)

- Integrated Summary of Safety (STN 125714/0.1, Module 5.3.5.3, received October 30, 2019)
- Draft Labeling Text (STN 125714/0.1, Module 1.14, received October 30, 2019)
- 3-Month Safety Update Report (STN 125714/0.19, Module 5.3.5.3, received March 16, 2020)
- Response to Information Request (IR) #24 regarding registry study protocol sample size (STN 125714/0.25, received April 3, 2020)
- Response to IR #32 regarding REMS Document edits (STN 125714/0.36, received May 1, 2020)
- Response to IR #35 regarding registry study protocol patient population and primary objective (STN 125714/0.36, received May 1, 2020)
- Response to IR #41 regarding REMS Supporting Document and tracking of Knowledge Assessment completion (STN 125714/0.37, received May 5, 2020)
- Response to IR #45 regarding clinical trial LTFU safety study milestones (STN 125714/0.42, received May 18, 2020)
- Response to IR #46 regarding registry study protocol target accrual and eligibility criteria (STN 125714/0.41, received May 13, 2020)
- Response to IR #50 regarding REMS Supporting Document Non-Compliance Action Plan (STN 125714/0.47, received June 9, 2020)
- Response to IR #68 regarding FDA edits to REMS materials and request to align REMS materials with final version of label (STN 125714/0.66, received September 10, 2020)

4 Summary of Prior Marketed Experience

Breyanzi is not marketed anywhere in the world.

5 Study Overview and Brief Description of Sponsor's Safety Database

Study 017001 is the pivotal study in this BLA application. Supportive safety data comes from three additional studies in the R/R third line or later (3L+) large B-cell lymphoma patient population: Studies JCAR017-BCM-001, JCAR017-BCM-002, and 017007. Data presented below are per the sponsor's report for the purpose of summarizing the safety database in this PVP review memorandum; see the OTAT clinical safety review memorandum for details of the FDA review findings.

5.1 Study 017001

Study 017001 is an ongoing U.S. Phase 1, single-arm, multicenter, multicohort, open label study of JCAR017 in adult subjects in two disease cohorts: diffuse large B-cell lymphoma (DLBCL) (N=269) and mantle cell lymphoma (N=17). The safety overview for this study focuses on the DLBCL cohort, consistent with the proposed label indication.

The primary objectives of the study are:

- To evaluate the safety of JCAR017 in adult subjects with R/R B-cell NHL, and
- To assess the antitumor activity of JCAR017.

Secondary objectives are related to assessing the rate of complete response and durability of antitumor activity of JCAR017, estimating progression-free and overall survival, characterizing the pharmacokinetic profile, and assessing health-related quality of life (HRQoL) and health economics and outcomes research.

Subjects are followed for safety, disease progression, and survival for two years after their last dose of JCAR017. Subjects are then enrolled in a separate LTFU study to monitor long-term safety, overall survival, and HRQoL for 15 years (Section 6.4, Long Term Follow-up Study).

Study Treatment

Study treatment consists of lymphodepleting chemotherapy (LDC) with fludarabine and cyclophosphamide for three days, followed two to seven days later by a single dose of JCAR017. Anticancer therapy between leukapheresis and LDC is allowed to control disease burden. The study includes dose-finding groups (DL1S, DL1D, DL2S, and DL3S) to evaluate and refine the dose and schedule of JCAR017 needed for safety and optimal antitumor activity (Table 2). Dose expansion groups (DL1D, DL2S, and DL3S) further assess the safety and efficacy of JCAR017, and the dose confirmation group (DL2S) evaluates the safety and efficacy of JCAR017 at the recommended regimen.

Table 2: Dose Regimens for Study 017001

Cohort	Dose	Number of Subjects Treated in DLBCL Cohort*
DL1S	50 × 10 ⁶ CAR+ T cells	45
DL1D	50 × 10 ⁶ CAR+ T cells on Day 1 and Day 15	6
DL2S	100 × 10 ⁶ CAR+ T cells, regimen selected by Steering Committee for further evaluation in dose confirmation study group	177
DL3S	150 × 10 ⁶ CAR+ T cells	41

*Sponsor's data cut-off August 12, 2019.

Study Population

The study population includes adults age 18 years and older with R/R B-cell NHL after at least two lines of therapy or after autologous hematopoietic stem cell transplant (auto-HSCT). The DLBCL cohort includes subjects with DLBCL, not otherwise specified (NOS; includes transformed DLBCL from indolent histology [tDLBCL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B (FL3B). The first subject was enrolled on January 6, 2016 (first treatment with JCAR017 occurred on February 22, 2016). As of the data cutoff (August 12, 2019), 269 subjects were treated with JCAR017 in the DLBCL cohort. The median study follow-up time is 11.5 months (range=0.2-35.0 months). Subjects in the DLBCL treated cohort have a median age=63 years (range=18-86 years) and the majority are male (n=174, 64.7%) and white (n=232, 86.2%). Subject dispositions are as follows: 103 with ongoing participation and 35 with study completion. An additional 131 subjects have discontinued from the study (121 deaths, seven withdrawal of consent, and two lost to follow-up).

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that started after JCAR017 infusion through 90 days following the final cycle of JCAR017; AEs occurring after initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy were not considered TEAEs. TEAEs were graded using the National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) version 4.03, except for cytokine release syndrome (CRS), which was graded based on the Lee criteria [1]. The majority of JCAR017 treated subjects in the DLBCL cohort experienced TEAEs (n=267, 99.3%). The most common TEAEs by preferred term (PT) included: neutropenia (n=169, 62.8%), anemia (n=129, 48.0%), fatigue (n=119, 44.2%), cytokine release syndrome (CRS) (n=113, 42.0%), nausea (n=90, 33.5%), and thrombocytopenia (n=84, 31.2%).

TEAEs Grade ≥ 3

The majority of JCAR017 treated subjects in the DLBCL cohort (n=213, 79.2%) experienced Grade ≥ 3 TEAEs. The most frequently reported Grade ≥ 3 TEAEs included neutropenia (n=161, 59.9%), anemia (n=101, 37.5%), thrombocytopenia (n=72, 26.8%), leukopenia (n=39, 14.5%), febrile neutropenia (n=24, 8.9%), hypophosphatemia (n=16, 5.9%), encephalopathy (n=12, 4.5%), and hypertension (n=12, 4.5%).

Treatment-emergent Serious Adverse Events

Nearly half (n=122, 45.4%) of subjects in the DLBCL treated cohort experienced a treatment-emergent serious adverse event (SAE). The most frequent treatment-emergent SAEs were CRS (n=44, 16.4%), encephalopathy (n=14, 5.2%), neutropenia (n=11, 4.1%), pyrexia (n=10, 3.7%), febrile neutropenia (n=10, 3.7%), thrombocytopenia (n=10, 3.7%), aphasia (n=9, 3.3%), pneumonia (n=8, 3.0%), confusional state (n=8, 3.0%), and hypotension (n=8, 3.0%).

Adverse Events of Special Interest

Adverse events of special interest (AESI) were pre-specified and included the following: CRS, investigator-identified neurotoxicity (iiNT), prolonged cytopenia, Grade ≥ 3 infection, hypogammaglobulinemia, infusion-related reaction (IRR), secondary malignancy, autoimmune disorder, tumor lysis syndrome (TLS), and macrophage activation syndrome (MAS) (Table 3). Due to the potential for late onset, the sponsor analyzed the AESIs of hypogammaglobulinemia, secondary malignancies, and autoimmune disorders, for the entire study period (i.e., treatment-emergent and post-treatment emergent periods) (Table 4).

Table 3: Treatment-emergent Adverse Events of Special Interest by Category and Grade*, Study 017001, DLBCL Treated Cohort†

Adverse Event of Special Interest	DLBCL Treated Cohort (N=269) n (%)
CRS or iiNT	127 (47.2)
Grade 3-4	29 (10.8)
Grade 5	0
CRS	113 (42.0)
Grade 3-4	6 (2.2)
Grade 5	0
iiNT	80 (29.7)
Grade 3-4	27 (10.0)
Grade 5	0
IRR	3 (1.1)
Grade 3-4	0
Grade 5	0
MAS	0
Grade 3-4	0
Grade 5	0
TLS	2 (0.7)
Grade 3-4	2 (0.7)
Grade 5	0
Infections, Grade ≥ 3	33 (12.3)
Grade 3-4	31 (11.5)
Grade 5	2 (0.7)
Grade ≥ 3 Cytopenia at Day 29 Visit	100 (37.2)

*CTCAE v4.03: Grade 1=mild; Grade 2=moderate; Grade 3=severe or medically significant but not immediately life-threatening; Grade 4= life-threatening; Grade 5=death.

†Adapted from Integrated Summary of Safety (ISS), Table 62.

Cytokine Release Syndrome

CRS was reported in 113 (42.0%) subjects in the DLBCL treated cohort; 107 (39.8%) subjects experienced Grade 1-2 CRS and 6 (2.2%) subjects experienced Grade 3-4 CRS; no subjects experienced Grade 5 CRS. Forty-four (16.4%) subjects experienced an SAE of CRS. Two subjects had ongoing CRS at the time of death (Subjects (b) (6) Appendix A); the investigators did not attribute death to CRS. The most frequently reported symptoms of CRS were pyrexia (n=107, 39.8%), hypotension (n=55, 20.4%), and tachycardia (n=47, 17.5%).

The median time to onset of first CRS was 5.0 days (range=1-14 days); median time to resolution of first CRS was 5.0 days (range=1-17 days). The median time to onset of the first Grade ≥ 3 CRS was 6.5 days (range=3-12 days); the median time to resolution of the first Grade ≥ 3 CRS was 6.0 days (range=5-15 days). Medications used for treatment of CRS included tocilizumab and/or corticosteroid (n=53, 19.7%), tocilizumab only (n=27, 10.0%), both tocilizumab and corticosteroids (n=21, 7.8%), vasopressors (n=7, 2.6%), and corticosteroids only (n=5, 1.9%).

Investigator Identified Neurologic Toxicity and Neurotoxicity Events of Special Interest

The sponsor defined iiNT as any investigator identified central nervous system (CNS) TEAE related to JCAR017. The sponsor grouped individual AEs associated with iiNT into eight neurotoxicity events of special interest (NESI) categories: encephalopathy, aphasia, tremor, delirium, dizziness, headache, anxiety, and insomnia. Other iiNT events of special interest included ataxia/gait disturbance, brain edema, seizure, cerebellar syndrome, mood disorder, motor dysfunction, visual disturbance, peripheral neuropathy, cognitive disorder, incontinence, and NOS.

iiNT were reported in 80 (29.7%) subjects in the DLBCL treated cohort; 53 (19.7%) subjects experienced Grade 1-2 iiNT, 27 (10.0%) experienced Grade 3-4 iiNT; no subjects experienced Grade 5 iiNT. The most frequently reported iiNT NESI categories were encephalopathy (n=57, 21.2%), aphasia (n=26, 9.7%), tremor (n=26, 9.7%), delirium (n=16, 5.9%), dizziness (n=11, 4.1%), and headache (n=9, 3.3%).

The median time to onset of the first iiNT was 9.0 days (range=1-66 days); median time to resolution of the first iiNT was 11.0 days (range=1-86 days). The median time to onset of the first Grade ≥ 3 iiNT was 9.0 days (range=2-44 days); the median time to resolution of the first Grade ≥ 3 iiNT was 12.0 days (range=3-83 days). Medications

used for treatment of iiNT included tocilizumab and/or corticosteroids (n=45, 16.7%), corticosteroids only (n=36, 13.4%), both tocilizumab and corticosteroids (n=8, 3.0%), other immunosuppressive agents (i.e., siltuximab and anakinra) (n=2, 0.7%), and tocilizumab only (n=1, 0.4%); some medications were given for treatment of concurrent CRS.

Thirty-nine (14.5%) subjects experienced an SAE of iiNT, including two subjects with seizures (Subjects (b) (6) and one subject with brain edema (Subject (b) (6), which are summarized below:

- Subject (b) (6), a 37-year-old American Indian-white female, experienced Grade 2 CRS, mild dizziness, and confusion on Day 12. A Grade 4 seizure with altered mental status occurred on Day 14; subsequent EEG showed non-convulsive status epilepticus. The subject was treated with antiseizure medications and steroids and transferred to a neuro-intensive care unit (ICU). The subject continued to deteriorate and could not speak or follow commands. The infectious disease work-up was negative. CRS resolved on Day 15. The subject remained with poor mental status and was intubated on Day 16. Seizure activity stopped per EEG on Day 17; the subject's mental status began to improve on Day 21. The subject was extubated on Day 23 and discharged home on Day 28. The subject was alive on Day 721.
- Subject (b) (6), a 29-year-old white male, developed Grade 3 TLS on Day 1 and Grade 1 CRS on Day 3; CRS worsened to Grade 4 by Day 9. The subject also experienced Grade 4 renal failure and respiratory failure on Day 9 and was intubated and started on daily dialysis. CRS resolved on Day 16; the same day the subject experienced a Grade 3 seizure. Grade 3 encephalopathy was diagnosed on Day 17. The encephalopathy improved to Grade 2 on Day 27. The subject experienced prolonged cytopenia on Day 29; thrombocytopenia continued on Day 50. The subject was discharged on Day 58 and died on Day 60 due to disease progression.
- Subject (b) (6), 50-year-old white male, experienced Grade 1 euphoric mood and insomnia on Day 1. He experienced Grade 1 CRS and Grade 1 derealization disorder on Day 2. A one-day episode of Grade 1 unilateral blindness and loss of right visual field occurred for a few minutes on Day 3. The subject became more somnolent, confused, and hypoxic and was transferred to the ICU. A brain MRI showed abnormal FLAIR signal within the right anterior temporal lobe and the right parasagittal posterior parietal lobe on Day 3; the subject was diagnosed with Grade 2 brain edema. The subject was treated with oxygen, acetazolamide sodium, dexamethasone, insulin, tocilizumab, and levetiracetam. The subject improved and was discharged from the ICU on Day 5. An additional brain MRI showed leptomeningeal enhancement in the right temporal region, thought to possibly be related to an infectious etiology, neoplastic involvement, or CRS/neurotoxicity on Day 12. The subject improved and the brain edema was considered resolved on Day 29. The subject had progressive disease confirmed on Day 89 and received a second JCAR017

infusion on Day 133. On Day 148 (re-treatment Day 16) a brain MRI confirmed disease progression. The subject continued anti-cancer treatments and died of disease progression on Day 309.

Seven subjects had ongoing iiNT at their time of death: four had encephalopathy and died of disease progression (Subjects (b) (6) [case discussed above]), one subject had somnolence and died of disease progression (Subject (b) (6)), one subject had agitation and died of pulmonary hemorrhage (Subject (b) (6) Appendix A), and one subject had a speech disorder and confusional state and died of progressive multifocal leukoencephalopathy (PML) (Subject (b) (6) Appendix A). No deaths were attributed to iiNT. In addition, one subject had an ongoing tremor at last study contact (Subject (b) (6)).

Prolonged Cytopenia

Cytopenia occurred in almost all subjects (n=248, 92.2%) in the DLBCL treated cohort between Days 1 and 29. Prolonged cytopenia was defined as Grade ≥ 3 cytopenia of neutropenia, thrombocytopenia, or anemia not resolved by Day 29, based on laboratory results. Prolonged cytopenia occurred in 100 subjects (37.2%) with 80 (29.7%) subjects having prolonged thrombocytopenia, 52 (19.3%) having prolonged neutropenia, and 17 (6.3%) having prolonged anemia. Recovery to Grade ≤ 2 cytopenia occurred by Day 90 in the majority of subjects who had laboratory results available: 9 of 11 (81.8%) subjects with anemia, 36 of 43 (83.7%) subjects with neutropenia, and 36 of 58 (62.1%) subjects with thrombocytopenia.

Infusion-related Reactions

IRR related to JCAR017 occurred in three (1.1%) subjects in the DLBCL treated cohort. All three events occurred on the day of infusion and were Grade 1 or 2. Subject (b) (6) a 57-year-old white male, experienced Grade 2 IRR with symptoms of lip swelling and abdominal itching. Subject (b) (6) , a 73-year-old white male, experienced Grade 1 IRR (signs and symptoms not reported). Subject (b) (6) , a 64-year-old white male, experienced Grade 1 IRR with symptoms of headache, flushing, and pruritis. Treatment for IRR was not reported. No IRR prevented the completion of JCAR017 infusion.

Macrophage Activation Syndrome

No cases of MAS were reported in Study 017001.

Tumor Lysis Syndrome

Two (0.7%) TLS events (both Grade 3; neither TLS event was an SAE) occurred in subjects in the DLBCL treated cohort. Subject (b) (6) (case discussed above in iiNT SAE section), a 29-year-old white male, experienced a Grade 3 TLS that began on Day

1 and ended on Day 5; treatment included rasburicase. Subject (b) (6) a 59-year-old white male, experienced Grade 3 TLS that began on Day 1 and ended on Day 30; treatment was not reported.

Infections

Many subjects (n=110, 40.9%) in the DLBCL treated cohort experienced an infection in the treatment-emergent period. Thirty-three (12.3%) experienced Grade ≥ 3 , including two subjects with Grade 5 infections (Appendix A). Infections were due to unspecified pathogens (n=22, 8.2%), bacterial pathogens (n=11, 4.1%), viral pathogens (n=4, 1.5%), and fungal pathogens (n=2, 0.7%). The most frequent infection-related PT was pneumonia (n=8, 3.0%); other TEAE infections occurred in less than 2% of subjects. Among subjects in the DLBCL cohort with a history of hepatitis B (n=11) or hepatitis C (n=2), none had TEAEs considered consistent with hepatitis B reactivation or worsening hepatitis C infection.

Secondary Malignancies, Hypogammaglobulinemia, and Autoimmune Disorders

Due to the potential for late onset, the sponsor analyzed the AESIs of hypogammaglobulinemia, secondary malignancies, and autoimmune disorders, for the entire study period (i.e., treatment-emergent and post-treatment emergent periods) (Table 4).

Secondary malignancies were defined as newly diagnosed cancers not considered to be a relapse of the underlying disease for which the subject received study treatment. Secondary malignancies included results from searches for standardized MedDRA queries (SMQs) for “pre-malignant disorders” and “malignancies” and were subject to subsequent medical review by an adjudication panel. Five (1.9%) subjects in the DLBCL treated cohort developed a secondary malignancy in the treatment-emergent period: one subject with peripheral T-cell lymphoma (Subject (b) (6)), one subject with myelodysplastic syndrome (MDS; Subject (b) (6)), one subject with cutaneous basal cell carcinoma (Subject (b) (6)), one subject with endometrial adenocarcinoma (Subject (b) (6)), and one subject with cutaneous squamous cell carcinoma in situ (Bowen’s disease; Subject (b) (6)). The individual (Subject (b) (6)) with peripheral T-cell lymphoma was further evaluated to assess the possibility of oncogenesis due to JCAR017. JCAR017 transgene was detected in biopsy specimens using a (b) (4)-based assay, however, results were considered inconsistent with a clonal CAR T-cell proliferative disorder or transgene-induced malignant transformation since circulating CAR T genome was still detectable in peripheral blood and CAR positive cells were polyclonal. Subsequent insertion site analysis (using a non-validated (b) (4) and (b) (4) method) did not reveal integration sites proximal to potentially oncogenic loci. Other secondary malignancies in the treatment-emergent period that

were tested for CAR T transgene were negative and study investigators did not assess other secondary malignancies as related to JCAR017.

Fifteen (6.1%) subjects in the DLBCL treated cohort experienced a secondary malignancy in the post-treatment emergent period. Five subjects experienced MDS (Subjects (b) (6) [Appendix A], and (b) (6) five subjects experienced basal cell carcinoma (Subjects (b) (6) , three subjects experienced cutaneous squamous cell carcinoma (Subjects (b) (6) one subject experienced squamous cell carcinoma of the lung (Subject (b) (6)), one subject experienced acute myeloid leukemia (Subject (b) (6) , one subject experienced a low-grade appendiceal mucinous neoplasm (Subject (b) (6) , and one subject experienced bladder transitional cell carcinoma (Subject (b) (6) . Subject (b) (6) experienced three of the above types of secondary malignancies (MDS, basal cell carcinoma, and cutaneous squamous cell carcinoma). None of the secondary malignancies in the post-treatment emergent period were assessed by investigators as related to JCAR017.

Autoimmune disorders were based on the sponsor's search for the high-level group term (HLGT) "autoimmune disorders" plus the following PTs: temporal arteritis, granulomatosis with polyangiitis, vasculitis, Behcet's syndrome, Basedow's disease, and erythema nodosum; subsequent medical review was conducted by an adjudication panel. One subject in the DLBCL treated cohort developed an AE initially reported as immune enteritis (Grade 1, autoimmune colitis) on Day 29, considered related to JCAR017. Upon further work-up the diagnosis was changed to nonspecific enteritis. There were no autoimmune disorders reported as post-treatment emergent AEs.

Table 4: Secondary Malignancies, Hypogammaglobulinemia, and Autoimmune Disorders in Treatment-emergent and Post-treatment Emergent Time Periods, Study 017001, DLBCL Treated Cohort*

Adverse Event of Special Interest	DLBCL Treated Cohort (N=269) n (%)
Treatment-emergent period	
N	269
Secondary malignancy	5 (1.9)
Grade \geq 3	2 (0.7)
Hypogammaglobulinemia	37 (13.8)
Grade \geq 3	0
Autoimmune disorders	1 (0.4)
Grade \geq 3	0
Post-treatment Emergent period†	
N	247
Secondary malignancy	15 (6.1)

Grade \geq 3	8 (3.2)
Hypogammaglobulinemia	12 (4.9)
Grade \geq 3	0
Autoimmune disorders	0
Grade \geq 3	0

*Adapted from ISS, Table 63.

†The post-treatment emergent period starts 91 days following the final cycle of JCAR017, or upon initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days following the final cycle of JCAR017.

Deaths

In the DLBCL cohort, 122 (45.4%) deaths were reported after the first JCAR017 treatment. Among those who died, the majority (n=105, 86.1%) died due to disease progression; 10 (8.2%) deaths were due to TEAEs (not including Subject (b) (6) who died after study completion; Appendix A), three (2.5%) deaths were due to other causes (i.e., stroke unrelated to study, pneumonia, and diffuse intra-abdominal ischemia), and four (3.3%) deaths were due to unknown causes. The majority of deaths (n=89, 73.0%) occurred more than 90 days after the last JCAR017 treatment. Nine deaths (7.4%) occurred within 30 days after the last JCAR017 treatment; six (4.9%) of these deaths were attributed to disease progression and three (2.5%) were attributed by investigator's to AEs.

Two deaths resulted in JCAR017 study protocol amendments. Subject (b) (6) (Appendix A) died from a non-vaso-occlusive cardiomyopathy. This subject was a 51-year-old American Indian female with a history of diabetes mellitus, obesity, hypothyroidism, renal insufficiency, and intermittent hypertension, anemia, and sinus tachycardia who had been previously treated with potentially cardiotoxic agents (i.e., doxorubicin, cyclophosphamide, ifosfamide, cisplatin, etoposide, and cytarabine). Prior to JCAR017 infusion, the subject had a left ventricular ejection fraction greater than 50%. The subject developed fever and hypotension after LDC and required antibiotics and dopamine; the subject was afebrile and off of dopamine for 24 hours before JCAR017 infusion. After JCAR017 infusion, the subject was stable until Day 4 when she was found unresponsive without pulse or respiration. The subject was resuscitated back to sinus rhythm and laboratory studies revealed an elevated troponin; an electrocardiogram (ECG) suggested an evolving anterior myocardial infarction and an echocardiogram showed severe cardiomyopathy with an ejection fraction of 20% and regional wall motion abnormalities in the distribution of the left anterior descending coronary artery. The subject's troponin and CKMB increased and her ECG showed an inferior infarct and prolonged QT. She developed multi-organ failure and died on Day 7. Autopsy revealed multifocal patchy subendothelial necrosis in the left ventricle and

interventricular septum, cardiomegaly, and left ventricular hypertrophy; the cause of death was cardiac failure due to non-vaso-occlusive cardiomyopathy. JCAR017 study protocols were amended to include a requirement for clinical stability prior to JCAR017 infusion (i.e., absence of suspected or active infection or fever, stable imaging results, controlled cardiac arrhythmias, without requirement of supplemental oxygen or vasopressors, and stable end organ function).

Subject (b) (6) (Appendix A) was a 74-year-old male who developed progressive weakness, confusion, bilateral vision loss, and multiple brain magnetic resonance imaging abnormalities with onset 6-weeks post-LDC (fludarabine and cyclophosphamide) and JCAR017 treatment. This subject had a serum creatinine of 2.3 mg/dL on Day 1 which increased to 3.4 mg/dL by Day 8; the increase was attributed to hypotension associated with CRS. The subject was treated with high doses of steroids, but the neurologic syndrome progressed and the subject expired 10-weeks after JCAR017 infusion due to the brain disorder. Autopsy revealed bilateral optic nerve axonal injury. The investigator attributed the death to fludarabine-induced leukoencephalopathy. The study protocol was amended to reinforce fludarabine dose reduction in subjects with renal impairment in accordance with the approved fludarabine product label.

5.2 Study JCAR017-BCM-001

Study JCAR017-BCM-001 is an ongoing Phase 2, open-label, single-arm, multicohort, multicenter, monotherapy study to determine the efficacy and safety of JCAR017 in adult subjects with R/R aggressive B-cell NHL after at least two lines of therapy or auto-HSCT. Subjects are followed for safety, disease progression, and survival for two years after their last dose of JCAR017. Subjects will then be enrolled in a separate LTFU safety study (Section 6.4, Long Term Follow-up Study).

Study treatment consists of LDC with fludarabine and cyclophosphamide for three days, followed two to seven days later with JCAR017 administered as a single dose of 100×10^6 CAR+ T cells. Subjects are enrolled in one of six cohorts; two cohorts include subjects with the proposed indication:

- Cohort 1 (Europe, N=21): Subjects with DLBCL NOS (de novo), DLBCL transformed from follicular lymphoma (tFL), high-grade lymphoma (HGL), and FL3B per WHO 2016 classification [2], after at least two lines of therapy, including an anthracycline and rituximab (or other CD20-targeted agents)
- Cohort 3 (Japan, N=10): Subjects meeting eligibility criteria for Cohort 1

The study began on June 5, 2018; 31 subjects have been treated as of the ISS data cut-off (August 1, 2019 for JCAR017-BCM-001). The median study follow-up time is 4.5 months (range=0.4-10.7 months). Subjects in cohorts 1 and 3 have a median age=58.0

years (range=40-73 years; younger than in Study 017001 where median age=63 years); the majority of subjects are male (n=19, 61.3%) and white (n=16, 51.6%).

All JCAR017 treated subjects in cohorts 1 and 3 experienced TEAEs (N=31, 100%), including 29 (93.5%) subjects with Grade ≥ 3 TEAEs and two (6.5%) subjects with Grade 5 (death) TEAEs (Appendix B; which includes Grade 5 TEAEs for all three supporting studies [BCM-001, BCM-002, and Study 017007]). AESIs of CRS or iiNT occurred in 16 (51.6%) subjects; 15 (48.4%) subjects experienced CRS and five (16.1%) experienced iiNT. Ten (32.3%) subjects experienced the AESI of prolonged cytopenia, four (12.9%) subjects had a Grade ≥ 3 infection, and two subjects developed MAS (6.5%; Subjects (b) (6) ; Appendix B); no subjects experienced TLS or IRR. No subjects in BCM-001 developed secondary malignancies.

One of the two subjects with MAS (Subject (b) (6) ; Appendix B) had a history of progressive DLBCL with a bulky tumor and a history of pulmonary embolism and ongoing deep vein thrombosis. This subject developed Grade 4 CRS on Day 7 (treated with tocilizumab, siltuximab, and, corticosteroids) and Grade 3 MAS, which progressed to Grade 4 MAS on Day 15. This subject expired from respiratory failure due to fungal pneumonia and *Candida krusei* sepsis on Day 15. After this subject's death, the study was paused and protocol amendments were instituted to reinforce the need for clinical stability prior to JCAR017 infusion and exclusions were added for subjects with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher (i.e., ambulatory and capable of all self-care but unable to carry out any work activities, or worse status).

5.3 Study JCAR017-BCM-002

Study JCAR017-BCM-002 (N=26) is an ongoing Phase 1 and 2, global, open-label, multi-arm, parallel, multicohort, multicenter, combination therapy study being conducted in the U.S. and Europe to evaluate the safety, tolerability, pharmacokinetics, efficacy, and HRQoL of a single-dose of JCAR017 in combination with additional immunotherapies in adults with R/R aggressive B-cell NHL disease after at least two lines of therapy or auto-HSCT.

The study includes two arms:

- *Arm A evaluates JCAR017 in combination with IV durvalumab*
 - *Arm A/Cohort 1A:*
 - *Day 1: JCAR017 infusion of 50×10^6 CAR+ T cells*
 - *Day 29 and 36: 375 mg durvalumab*
 - *Day 43: 750 mg durvalumab*
 - *Day 57 and 85: 1500 mg durvalumab*
 - *Arm A/Cohort 1B:*
 - *Day 1: JCAR017 infusion of 100×10^6 CAR+ T cells*

- Day 29 and 36: 375 mg durvalumab
- Day 43: 750 mg durvalumab
- Day 57 and 85: 1500 mg durvalumab
- Arm B evaluates JCAR017 in combination with oral CC-122
 - Arm B/Cohort 1A:
 - Day 1: JCAR017 infusion of 100×10^6 CAR+ T cells
 - Day 29 to 180: 2 mg CC-122 on 5 out of 7 days

Subjects are followed for safety, disease progression, and survival for two years after their last dose of JCAR017. Subjects will then be enrolled in a separate LTFU safety study (Section 6.4, Long Term Follow-up Study). Safety data in the ISS does not include AEs occurring after the start of combination therapy (Day 29), except for deaths, secondary malignancies, autoimmune disorders, and hypogammaglobulinemia.

The study began November 28, 2017; 26 subjects have been treated as of the data cut-off (August 1, 2019 for JCAR017-BCM-002). Median study follow-up time is 7.2 months (range=0.8-18.7 months). Subjects have a median age=66.0 years (range=27-83 years; subjects tended to be older than in Study 017001 where median age=63 years); the majority of subjects are male (n=19, 73.1%) and white (n=24, 92.3%).

All JCAR017 treated subjects in BCM-002 experienced TEAEs (N=26, 100%), including 19 (73.1%) subjects with Grade ≥ 3 TEAEs and two (7.7%) subjects with Grade 5 (death) TEAEs (Appendix B). One (3.8%) subject in BCM-002 experienced a Grade 5 TEAE in the post-treatment emergent period. CRS or iiNT occurred in 11 (42.3%) subjects; 10 subjects (38.5%) experienced CRS and six (23.1%) subjects experienced iiNT. Eight (30.8%) subjects experienced prolonged cytopenia, five (19.2%) subjects had a Grade ≥ 3 infection, and one subject experienced an IRR (3.8%); no subjects experienced TLS or MAS. One (3.8%) subject developed colon carcinoma in situ (Subject (b) (6); Appendix B) in the treatment-emergent period and two (10.5%) subjects (Subjects (b) (6)) developed cutaneous squamous cell carcinoma in the post-treatment emergent period. None of the secondary malignancies were assessed by investigators as related to JCAR017.

5.4 Study 017007

Study 017007 is an ongoing Phase 2, open-label, single-arm, multicenter, monotherapy study to determine the efficacy and safety of JCAR017 in adult subjects with R/R large B-cell lymphoma after at least two systemic lines of therapy or auto-HSCT. The study is being conducted in the U.S. in the outpatient setting at non-tertiary care centers. Subjects include individuals with DLBCL NOS, tFL, HGL, DLBCL transformed from indolent NHL (tiNHL), PMBCL, and FL3B.

Study treatment consists of LDC with fludarabine and cyclophosphamide for three days, followed two to seven days later with JCAR017 administered as a single dose of $100 \times$

10⁶ CAR+ T cells. Subjects will be followed for safety, disease progression, and survival for two years after their last dose of JCAR017. Subjects will then be enrolled in a separate LTFU safety study (Section 6.4, Long Term Follow-up Study).

The study began November 29, 2018; 17 subjects have been treated as of the data cut-off (August 1, 2019 for Study 017007). Median study follow-up time is 2.7 months (range=0.1-5.0 months). Subjects have a median age=68.0 years (range=43-81 years; subjects tended to be older than in Study 017001 where median age=63 years); the majority of subjects are male (n=11, 64.7%) and white (n=15, 88.2%).

All JCAR017 treated subjects experienced TEAEs (n=17, 100%), including 15 (88.2%) subjects with a Grade \geq 3 TEAE; no subjects experienced a Grade 5 (death) TEAE. CRS or iiNT occurred in seven (41.2%) subjects; six (35.3%) subjects experienced CRS and four (23.5%) subjects experienced iiNT. Three (17.6%) subjects experienced prolonged cytopenia, and two (11.8%) subjects had a Grade \geq 3 infection. No subjects experienced IRR, TLS, or MAS. No subjects experienced secondary malignancies. No deaths have been reported as of the data cut-off date.

6 Pharmacovigilance Plan

6.1 Summary of Pharmacovigilance Plan

The sponsor submitted a PVP proposing routine pharmacovigilance (PV) activities in accordance with 21 Code of Federal Regulations (CFR) 600.80 including submission of adverse event reports and periodic safety update reports (PSURs), a Risk Evaluation and Mitigation Strategy (REMS), a post-marketing registry study (JCAR017-DLBCL-001), a LTFU study (GC-LTFU-001), and a transgene assay service (Table 5).

Table 5: Summary of Safety Concerns and Planned Pharmacovigilance Activities*

Safety Concern	Proposed Pharmacovigilance Activities	Objectives and Rationale
Important Identified Risks		
Cytokine release syndrome (CRS)	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none">• Adverse event (AE) reporting• SAE follow-up• Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none">• REMS• Post-marketing registry study (JCAR017-DLBCL-001)	<p>To evaluate and monitor the reporting rate and severity of CRS using post-marketing spontaneous reports.</p> <p>To evaluate and monitor the incidence and severity of Grade ≥ 3 CRS in the post-marketing registry study.</p>
Neurologic toxicity (NT)	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none">• AE reporting• SAE follow-up• Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none">• REMS	<p>To evaluate and monitor the reporting rate and severity of NT using post-marketing spontaneous reports.</p> <p>To evaluate and monitor the incidence and severity of Grade ≥ 3 neurotoxicity in the post-marketing registry study.</p>

	<ul style="list-style-type: none"> Post-marketing registry study (JCAR017-DLBCL-001) 	
Infections	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> AE reporting SAE follow-up Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing registry study (JCAR017-DLBCL-001) 	<p>To evaluate and monitor the reporting rate of infections using post-marketing spontaneous reports.</p> <p>To evaluate and monitor the incidence and severity of Grade > 3 infections in the post-marketing registry study.</p>
Hypogammaglobulinemia	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> AE reporting SAE follow-up Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing registry study (JCAR017-DLBCL-001) 	<p>To evaluate and monitor the reporting rate of hypogammaglobulinemia AEs using post-marketing spontaneous reports.</p> <p>To evaluate and monitor the incidence and severity of Grade > 3 hypogammaglobulinemia in the post-marketing registry study.</p>
Macrophage activation syndrome (MAS)	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> AE reporting SAE follow-up Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing registry study (JCAR017-DLBCL-001) 	<p>To evaluate and monitor the reporting rate and severity of MAS using post-marketing spontaneous reports.</p> <p>To evaluate and monitor the incidence and severity of Grade > 3 MAS in the post-marketing registry study.</p>
Tumor lysis syndrome (TLS)	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> AE reporting SAE follow-up Signal detection <p>Additional pharmacovigilance activities:</p>	<p>To evaluate and monitor the reporting rate and severity of TLS using post-marketing spontaneous reports.</p>

	<ul style="list-style-type: none"> Post-marketing registry study (JCAR017-DLBCL-001) 	To evaluate and monitor the incidence and severity of Grade > 3 TLS in the post-marketing registry study.
Cytopenias	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> AE reporting SAE follow-up Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing registry study (JCAR017-DLBCL-001) LTFU study (GC-LTFU-001) 	<p>To evaluate and monitor the reporting rate and severity of cytopenia AEs using post-marketing spontaneous reports.</p> <p>To evaluate and monitor the incidence and severity of prolonged cytopenias in the post-marketing registry study.</p> <p>To evaluate and monitor the severity and incidence of cytopenias in the post-clinical trial setting (LTFU study).</p>
Important Potential Risks		
Autoimmune disorders	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> AE reporting SAE follow-up Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing registry study (JCAR017-DLBCL-001) LTFU study (GC-LTFU-001) 	<p>To evaluate and monitor the reporting rate and severity of autoimmune disorders using post-marketing spontaneous reports.</p> <p>To evaluate and monitor the incidence and severity of autoimmune disorders in the post-marketing registry study.</p> <p>To evaluate and monitor the incidence and severity of autoimmune disorders in the post-clinical trial setting (LTFU study).</p>
Graft versus host disease (GvHD)	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> AE reporting SAE follow-up Signal detection 	To evaluate and monitor the reporting rate and severity of GvHD using post-marketing spontaneous reports.

	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • None proposed 	
Secondary malignancies and insertional mutagenesis	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> • AE reporting • SAE follow-up • Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Targeted questionnaires for secondary malignancies • Post-marketing registry study (JCAR017-DLBCL-001) • LTFU study (GC-LTFU-001) • Transgene assay service available as applicable 	<p>To evaluate and monitor the reporting rate of all secondary malignancies using post-marketing spontaneous reports.</p> <p>To collect additional information on reported cases of secondary malignancies utilizing a targeted questionnaire.</p> <p>To test secondary malignancies of T-cell origin for JCAR017 transgene levels and, if applicable, insertional oncogenesis in the post-marketing setting from both the registry study and spontaneous reports.</p> <p>To test secondary malignancies for JCAR017 transgene levels and, if applicable, insertional oncogenesis in the post-clinical trial setting (LTFU study).</p>
Missing Information		
Impact on pregnancy and lactation	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> • AE reporting • SAE follow-up • Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing registry study (JCAR017-DLBCL-001) • LTFU study (GC-LTFU-001) 	<p>To evaluate the effect of JCAR017 on pregnancy outcomes for both mother and child using post-marketing spontaneous reports.</p> <p>To evaluate the effect of JCAR017 on pregnancy outcomes for both mother and child in the post-marketing registry study.</p> <p>To evaluate the long-term effect of JCAR017 on pregnancy outcomes for both mother and child in the post-clinical trial setting (LTFU study).</p>

Long-term safety	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> • AE reporting • SAE follow-up • Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing registry study (JCAR017-DLBCL-001) • LTFU study (GC-LTFU-001) 	<p>To evaluate the reporting rates and severity of JCAR017 AEs using post-marketing spontaneous reports.</p> <p>To evaluate the incidence and severity of other AEs Grade >3 considered related to JCAR017 treatment in the post-marketing registry study.</p> <p>To assess long-term safety in the post-clinical trial setting (LTFU study).</p>
Safety in pediatrics	<p>Routine pharmacovigilance activities:</p> <ul style="list-style-type: none"> • AE reporting • SAE follow-up • Signal detection <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • LTFU study (GC-LTFU-001) 	<p>To evaluate the long-term safety of JCAR017 in pediatric patients in the post-marketing setting.</p> <p>To assess the effect of growth, developmental outcomes, and sexual maturity status for subjects who were aged < 18 years at the time of GM T-cell treatment (LTFU study).</p>

*Excerpted from sponsor's Pharmacovigilance Plan, Version 1.0, Table 2: PVP by Safety Issue.

6.2 Risk Evaluation and Mitigation Strategy (REMS)

The sponsor proposes a REMS program to ensure that the benefits of the drug outweigh the risks. The goal of the REMS is to mitigate the risks of CRS and NT by:

- Ensuring hospitals and associated clinics that dispense Breyanzi are specially certified and have immediate access to tocilizumab, and
- Ensuring that those who prescribe, dispense, or administer Breyanzi are aware of how to manage the risks of CRS and NT.

The REMS program includes the following elements to ensure safe use (ETASU):

- Healthcare facilities that dispense and administer Breyanzi must be enrolled in the REMS and comply with REMS requirements,
- Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within two hours after Breyanzi infusion, if needed for treatment of CRS, and
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer Breyanzi are trained on the management of CRS and NT.

The REMS implementation system includes:

- Validated, secure database of all Breyanzi REMS Certified Care Centers to document and support implementation of REMS elements,
- REMS Non-compliance Action Plan and audit plan for hospitals and associated clinics to ensure all REMS processes and procedures are in place and being followed,
- REMS call center for REMS participants,
- REMS Live Training Program and Knowledge Assessment (KA),
- Patient wallet card detailing signs and symptoms of severe or life-threatening side effects, highlighting need to alert any healthcare provider of Breyanzi treatment, and advising patients to stay within two hours of treatment location for at least four weeks after receiving Breyanzi, and
- Dedicated website that provides information on the product, full prescribing information, warnings associated with use of the product, and overview of Breyanzi REMS.

In addition, Breyanzi REMS certified sites are required to report any serious^a AEs suggestive of CRS or NT to the REMS Program.

^a As defined in 21CFR600.80, an adverse experience is “serious” if it results in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Reviewer comment: Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the product outweigh the risks. DE review of the sponsor's proposed REMS incorporated input from the Center for Drug Evaluation and Research (CDER) Division of Risk Management (DRM) and the Office of the Chief Counsel (OCC). DE presented the REMS program to the CBER Safety Working Group (SWG) on May 14, 2020. It was determined that a REMS with ETASU is necessary to ensure the benefits of Breyanzi outweigh the risks of CRS and NT, which can include fatal or life-threatening reactions. The sponsor submitted a REMS with ETASU in the BLA application. An IR was sent to request edits to the REMS Document to maintain consistency and align the REMS program with those of other approved CAR T-cell products. The sponsor's IR response and revised REMS Document are acceptable.

The sponsor also submitted a Supporting REMS Document which includes a Breyanzi REMS Assessment Plan and Non-compliance Action Plan. The sponsor will audit all Breyanzi REMS Certified Care Centers no later than 180 calendar days after the Breyanzi REMS Certified Care Center places its first order of Breyanzi. The sponsor will submit REMS assessment reports to FDA at 6 months, 12 months, and then annually thereafter. An IR was sent to request edits to the REMS Non-compliance Action Plan to further outline the purpose of the plan, provide examples of non-compliance events, and clarify roles, responsibilities and processes. The sponsor's IR response and revised Supporting REMS Document are acceptable.

In addition, the sponsor submitted REMS materials (i.e., Hospital Enrollment Form, REMS Live Training slides, patient wallet card, and KA) which were reviewed. The sponsor confirmed in an IR response that they will track completion of KAs using a central online database which will include KAs completed online, or on paper and emailed or faxed to the sponsor. FDA requested that the content of the REMS materials be aligned with content and language agreed to in the final label.

The sponsor will also conduct knowledge, attitudes, and behavior (KAB) surveys; the methodology and KAB protocols and survey instruments will be submitted for FDA review at least 90 days before initial survey administration. KAB survey results will be submitted in the REMS assessment reports at years 2, 5, and 7.

6.3 Post-Marketing Registry Study

The sponsor proposes a post-marketing registry study (JCAR017-DLBCL-001) with the primary objective to characterize the incidence and severity of selected AEs in patients treated with Breyanzi in the post-marketing setting and to monitor for additional clinically

important events not yet identified as part of the Breyanzi safety profile. The secondary objective is to assess overall survival in patients treated with Breyanzi in the post-marketing setting.

The primary safety endpoint is incidence and severity of the following AEs post-Breyanzi infusion:

- All secondary malignancies,
- CRS Grade ≥ 3 ,
- Neurotoxicity Grade ≥ 3 ,
- Prolonged cytopenia,
- Pregnancy outcome, and
- Other AEs Grade ≥ 3 considered related to Breyanzi treatment (e.g., TLS, B-cell aplasia, infections, and hypogammaglobulinemia).

The study protocol states that secondary malignancies must be reported to the sponsor by treating physicians within 72 hours of awareness of diagnosis in order to expedite AE reporting and to initiate a separate non-protocol-related process for tumor specimen processing and testing for the JCAR017 vector sequence in the case of secondary malignancy of T-cell origin.

The study will include patients from existing independent registries (e.g., Center for International Blood and Marrow Transplant Research and European Group for Blood and Marrow Transplantation) and will enroll 1000 patients over a 5-year period. Patients will be followed for up to 15 years.

The sponsor proposes the following milestones:

- Final protocol submission: January 31, 2021
- Study completion: Q1 2041
- Final study report: Q2 2042

Reviewer comment: The sponsor submitted a draft protocol and draft statistical analysis plan for the registry study (Received October 30, 2019; STN 125714/0.1, Module 1.16.1). Breyanzi has potential for the serious risk of secondary malignancy due to replication-competent retrovirus or insertional mutagenesis. As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the serious risk of secondary malignancy associated with Breyanzi. As outlined in the Sentinel sufficiency memorandum (please see attached), the CBER Sentinel Team has determined that CBER Sentinel will not be sufficient to characterize the serious risk of secondary malignancy since 15 years of follow-up and collection of tissue samples are needed; this is not feasible in a claims-based system such as Sentinel. Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, the sponsor will be required to

conduct a PMR safety study under FDAAA Title IX to identify the serious risk of secondary malignancy. The PMR will be conducted for up to 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020). Similar PMR safety studies have been required for approved CAR T-cell products.

IRs were sent requesting that the registry study sample size be increased from 1000 patients to 1500 patients since secondary malignancy is expected to be a rare event and to align with PMR studies for other approved CAR T-cell products. The sponsor's IR response proposes to increase the registry study sample size to 1500 patients, of which 500 patients will be from ongoing and planned JCAR017 clinical trials. While this is acceptable, the sponsor was asked to confirm that these 500 patients will also remain in the LTFU study (in addition to the registry study) and will be representative of the patient population treated under this BLA. The sponsor's subsequent IR responses included a revised registry study protocol indicating that the study will include a total of 1500 patients, including at least 1000 patients treated with JCAR017 in the post-marketing setting and approximately 500 patients with large B-cell lymphoma who received at least two prior lines of therapy and were enrolled and treated with JCAR017 in ongoing and planned JCAR017 interventional clinical trials and, as applicable, asked to follow-up for a total of 15 years in a long-term follow up study. The sponsor's IR response is acceptable.

The sponsor was also asked to revise the primary objective in the draft registry protocol to include characterizing the incidence and severity of selected AEs, including secondary malignancy, in patients treated with JCAR017; the primary objective was revised as requested and is acceptable.

6.4 Long-Term Follow-Up Study

The sponsor is conducting a prospective, non-interventional, LTFU study (Study GC-LTFU-001; IND 16506) of all pediatric and adult subjects exposed to a gene-modified T-cell (GM T-cell) therapy in a Celgene sponsored, or Celgene alliance partner, sponsored clinical trial. The primary objectives of the study are to:

- Assess the risk of delayed AEs following exposure to GM T-cells, including:
 - New malignancies
 - New neurologic disorder, or exacerbation of pre-existing neurologic disorder
 - New rheumatologic or autoimmune disorder, or exacerbation of prior rheumatologic or other autoimmune disorder
 - New hematologic disorder
 - Other new clinical conditions considered related to prior GM T-cell therapy by the investigator
- Monitor for long-term persistence of GM T-cells, including analysis of vector integration sites, as appropriate,

- Monitor for generation of replication-competent lentiviruses/retroviruses (RCL/RCR),
- Assess long-term efficacy following treatment with GM T-cells,
- Describe growth, developmental outcome, and sexual maturity status for subjects aged < 18 years at time of GM T-cell therapy, and
- Assess long term HRQoL following treatment with GM T-cells.

Patient follow-up will consist of safety assessments (i.e., clinical history, focused physical exam, height, weight, delayed AE or SAE ascertainment), laboratory evaluations for persistent vector sequences (PVS) and RCR, and completion of patient-reported outcome (PRO) questionnaires (collected using PRO instruments from parent treatment protocol). If a patient's laboratory results for both PVS and RCR are undetectable at five years, then the patient may conclude in-person study assessments; patients will continue to be contacted for health status and AEs for up to 15 years. If a patient has a detectable result for either PVS or RCR at five years, then the patient will continue to be followed with annual PVS and RCR testing for up to 15 years or until both test results are undetectable. All SAEs thought to be related to prior GM T-cell therapy, including any confirmed detectable result from RCR testing, must be reported to the sponsor within 24 hours of the investigator's knowledge of the event. Patients will be followed for up to 15 years after the last JCAR017 infusion, until study withdrawal, loss to follow-up, or death, whichever occurs first. Pediatric subjects must reach Stage 5 per Tanner Staging Criteria prior to study discontinuation.

As of the data cut-off of August 12, 2019, a total of 29 subjects from Study 017001 (26 subjects from DLBCL cohort) have enrolled in the LTFU study. Median age=64 years (range=39-79 years), 19 (65.5%) are male, and most are white (93.1%). One SAE of basal cell carcinoma (Subject (b) (6)) has been reported, which the investigator considered unrelated to JCAR017. Transgene assay was not performed on the tumor tissue which was excised for cure.

Reviewer comment: The sponsor submitted an original protocol (STN 125714/0.1, Received October 30, 2019). The RCR testing schedule is in accordance with FDA Guidance for Industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-Up (January 2020). The LTFU study will be conducted for up to 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020).

The sponsor submitted a Development Safety Update Report (DSUR) (STN 16506/0.550, received August 22, 2019) which indicated the JCAR017 LTFU data are combined as appropriate with parent study data on a yearly or ad-hoc basis to fulfill Health Authority requests, as applicable and for final analysis. The first site was activated on February 7, 2018 and the first subject first visit (previously treated with

JCAR017) was August 21, 2018. The study has enrolled 25 patients as of June 25, 2019 (all from Study 017001). No delayed AEs were reported in the DSUR.

An IR was sent to request study milestones. The sponsor's IR response indicated that current milestones for the GC-LTFU-001 protocol, including projected enrollment of JCAR017-treated 3L+ large B-cell lymphoma in ongoing parent clinical trials include:

Last Subject Visit: August 17, 2038

Final Database Lock: September 30, 2038

Summary of completed GC-LTFU-001 follow-up of 3L+ large B-cell lymphoma JCAR017-treated subjects in the DSUR, Section 8.1: August 2039.

6.5 Transgene Assay Service

The sponsor proposes testing for JCAR017 transgene on all secondary malignancies where tissue is available in Study GC-LTFU-001. For the post-marketing registry study and post-marketing commercial use, transgene testing will be performed for all secondary malignancies of T-cell origin. The sponsor will assist prescribers who report AEs of secondary malignancies of T-cell origin with coordinating transfer of patient tumor samples for JCAR017 transgene testing. The product label will include a toll-free telephone number for AE reporting and tumor sample testing. The PVP states that *if JCAR transgene levels are detected in the tumor biopsy by in situ hybridization, and suggest malignant transformation due to insertional oncogenesis, insertion site analysis will also be performed to identify the transgene location and clonality of the insertion.*

7 DE Assessment of Sponsor's Pharmacovigilance Plan

7.1 Important Identified Risk: Cytokine release syndrome

CRS is known to be associated with CAR T-cell therapies and is a diagnosis of exclusion; there are no definitive diagnostic imaging or laboratory tests. CRS can cause fatal or life-threatening reactions; symptoms include fever, hypotension, tachycardia, hypoxia, and chills. Investigators were formally trained in the recognition and management of CRS in all JCAR017 studies.

Across the four JCAR017 studies summarized in this memorandum (N=343), CRS occurred in 144 (42.0%) subjects receiving JCAR017, including eight (2.3%) subjects with CRS Grade ≥ 3 . The median time to onset was 5 days (range=1-14 days); median time to resolution was 5 days (range=1-17 days). Four subjects had ongoing CRS at the time of death; none of the deaths were attributed to CRS (deaths attributed to pulmonary hemorrhage, septic shock, respiratory failure, and staphylococcal sepsis). Treatment for CRS included tocilizumab, corticosteroids, vasopressors, supplemental oxygen, and empirical treatment with antibiotics. Sixty-eight (19.8%) subjects received

tocilizumab and/or corticosteroid for CRS, 38 (11.1%) received tocilizumab only, 25 (7.3%) received tocilizumab and a corticosteroid, and five (1.5%) received corticosteroids only.

Reviewer comment: The important identified risk of CRS, which can be fatal or life-threatening, will be mitigated through a REMS with ETASU, PMR registry study, product labeling, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the U.S. Package Insert (USPI):

- *Boxed Warning: Cytokine Release Syndrome and Neurologic Toxicities*
- *Section 2.3, Management of Severe Adverse Reactions: Cytokine Release Syndrome*
- *Section 5.1, Warnings and Precautions: Cytokine Release Syndrome*
- *Section 5.3, Breyanzi REMS*
- *Section 6.1, Clinical Trials Experience*

The proposed PVP is appropriate to mitigate the risk of CRS.

7.2 Important Identified Risk: Neurologic toxicity

NT is known to be associated with CAR T-cell therapies and can be severe or life-threatening; NT is a diagnosis of exclusion and can occur as CRS is resolving, after CRS resolution, or in the absence of CRS. Investigators were formally trained in the recognition and management of NT, including the importance of excluding other potential causes of neurologic symptoms (e.g., stroke, meningitis, metabolic encephalopathy) in all JCAR017 studies.

Across the four JCAR017 studies summarized in this memorandum (N=343), iINT occurred in 95 (27.7%) subjects, including 34 (9.9%) subjects with Grade ≥ 3 events; no Grade 5 AEs were attributed to iINT. The most common NTs were encephalopathy (18.7%), tremor (9.3%), aphasia (9.0%), delirium (5.2%), dizziness (3.8%), and headache (3.2%). The median time to onset was 9 days post-JCAR017 infusion (range=1-66 days). The median time to resolution of NT was 9.5 days (range=1-86 days).

Reviewer comment: The important identified risk of NT, which can be fatal or life-threatening, will be mitigated through a REMS with ETASU, PMR registry study, product labeling, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- *Boxed Warning: Cytokine Release Syndrome and Neurologic Toxicities*
- *Section 2.3, Management of Severe Adverse Reactions: Neurologic Toxicity*
- *Section 5.2, Warnings and Precautions: Neurologic Toxicity*
- *Section 5.3, Breyanzi REMS*
- *Section 6.1, Clinical Trials Experience*

The proposed PVP is appropriate to mitigate the risk of NT.

7.3 Important Identified Risk: Infections

Many subjects receiving JCAR017 in clinical trials had risk factors for infection, including hypogammaglobulinemia, neutropenia, or lymphopenia (Section 7.4 Hypogammaglobulinemia and Section 7.7 Cytopenia). Across the four JCAR017 studies summarized in this memorandum (N=343), 133 (38.8%) subjects had any grade of infection during the treatment-emergent period, including 44 (12.8%) subjects with a Grade ≥ 3 infection. Thirty (8.7%) subjects had Grade ≥ 3 infections with unspecified pathogens, 14 (4.1%) had Grade ≥ 3 bacterial infections, four (1.2%) had Grade ≥ 3 fungal infections, and four (1.2%) had Grade ≥ 3 viral infections. Five (1.5%) treatment-emergent Grade 5 infections occurred, including two subjects (both of whom were in Study BCM-001 and also had MAS) whose infections were considered JCAR017-related by investigators: one subject with a JCAR017-related Candida sepsis and one subject with JCAR017-related respiratory failure who had ongoing Grade 4 JCAR017-related Candida sepsis and pulmonary mycosis at the time of death.

Reviewer comment: The important identified risk of infections, which can be fatal or life-threatening, will be mitigated through a PMR registry study, product labeling, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- *Section 5.5, Warnings and Precautions: Serious Infections*
- *Section 6.1, Clinical Trials Experience*

The proposed PVP is appropriate to mitigate the risk of infections.

7.4 Important Identified Risk: Hypogammaglobulinemia

Hypogammaglobulinemia is an on-target pharmacodynamic effect that is anticipated due to the JCAR017 mechanism of action. Across the four JCAR017 studies summarized in this memorandum (N=343), 41 (12.0%) subjects experienced hypogammaglobulinemia in the treatment-emergent period and 14 (4.7%) subjects experienced hypogammaglobulinemia in post-treatment-emergent period; none were Grade ≥ 3 .

Reviewer comment: The important identified risk of hypogammaglobulinemia will be mitigated through a PMR registry study, product labeling, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- *Section 5.7, Warnings and Precautions: Hypogammaglobulinemia*
- *Section 6.1, Clinical Trials Experience*

The proposed PVP is appropriate to mitigate the risk of hypogammaglobulinemia.

7.5 Important Identified Risk: Macrophage activation syndrome

MAS has been observed in association with approved anti-CD19 CAR T-cell therapies and can be life-threatening; MAS has been attributed to excess activation of CD8 T lymphocytes [3]. Across the four JCAR017 studies summarized in this memorandum (N=343), one subject in Study BCM-001 developed Grade 4 MAS and subsequently died the same day of JCAR017-related respiratory failure with ongoing Candida sepsis and pulmonary mycosis. A second subject in Study BCM-001 died of Candida sepsis (and progressive disease) with ongoing erythrophagocytosis consistent with Grade 4 MAS.

Reviewer comment: The important identified risk of MAS will be mitigated through a PMR registry study and routine pharmacovigilance activities. Due to the rare occurrence of MAS, the proposed PVP is appropriate to mitigate the risk of MAS.

7.6 Important Identified Risk: Tumor lysis syndrome

TLS is a condition that occurs when cancer cells die rapidly and release large amounts of potassium, phosphate, and uric acid into the blood. TLS can lead to cardiac conduction abnormalities, seizures, and acute kidney injury. Across the four JCAR017 studies summarized in this memorandum (N=343), TLS occurred in two subjects (both Grade 3 AEs) in pivotal Study 017001 (0.6%); no cases were observed in the supporting studies.

Reviewer comment: The important identified risk of TLS will be mitigated through a PMR registry study and routine pharmacovigilance activities. Due to the rare occurrence of TLS, the proposed PVP is appropriate to mitigate the risk of TLS.

7.7 Important Identified Risk: Cytopenia

Cytopenia is expected to occur in patients with DLBCL receiving LDC with fludarabine and cyclophosphamide prior to JCAR017 infusion. Across the four JCAR017 studies summarized in this memorandum (N=343), Grade ≥ 3 cytopenia occurred in almost all subjects (n=312, 91.0%). Prolonged cytopenia (any Grade ≥ 3 cytopenia present on Day 29) occurred in 121 (35.3%) subjects with 99 (28.9%) having prolonged thrombocytopenia, 63 (18.4%) having prolonged neutropenia, and 18 (5.2%) having prolonged anemia. Most subjects recovered from prolonged cytopenia by Day 90.

Reviewer comment: The important identified risk of cytopenia will be mitigated through a PMR registry study, a LTFU safety study for clinical trial subjects, product labeling, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- *Section 5.7, Warnings and Precautions: Prolonged Cytopenias*

- *Section 6.1, Clinical Trials Experience*

The proposed PVP is appropriate to mitigate the risk of cytopenia.

7.8 Important Potential Risks: Autoimmune disorders

Per the FDA Guidance for Industry: *Long-Term Follow-Up After Administration of Human Gene Therapy Products* (January 2020), transgenes encoding immune recognition factors may introduce the risk for autoimmune-like reactions upon prolonged exposure. One subject in Study 017001 was initially reported as having developed a Grade 1 autoimmune colitis; upon further work-up the diagnosis was changed to nonspecific enteritis. Across the four JCAR017 studies summarized in this memorandum (N=343), no subjects developed an autoimmune disorder.

Reviewer comment: The important identified risk of autoimmune disorders will be mitigated through a PMR registry study, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. The proposed PVP is appropriate to mitigate the risk of autoimmune disorders.

7.9 Important Potential Risks: Graft versus host disease

The proposed Breyanzi label and REMS training materials indicate that infusion of Breyanzi should be delayed if the patient has unresolved serious adverse reactions from preceding chemotherapies, active uncontrolled infection, or active GvHD. There is also a concern that modified T-cells, generated after Allo-SCT could lead to GvHD [4]. The AE listings from the sponsor show one subject (Subject (b) (6), a 72-year-old white female) in Study 017001 who had Grade 1 gastrointestinal and skin GvHD approximately eight months following JCAR017 infusion. This subject was recovering from GvHD, which investigators considered JCAR017-related. The sponsor did not otherwise report GvHD in the JCAR017 pivotal study or three supporting studies.

Reviewer comment: The important identified risk of GvHD will be mitigated through routine pharmacovigilance activities, product labeling, and a REMS Live Training program indicating to delay infusion of Breyanzi if the patient has active GvHD. The proposed PVP is appropriate to mitigate the potential risk of GvHD.

7.10 Important Potential Risks: Secondary malignancies and insertional mutagenesis

Across the four JCAR017 studies summarized in this memorandum (N=343), six (1.7%) subjects experienced secondary malignancy in the treatment-emergent period, including five (1.5%) subjects in Study 017001 (one peripheral T-cell lymphoma, one MDS, one cutaneous basal cell carcinoma, one endometrial adenocarcinoma, and one cutaneous

squamous cell carcinoma in situ) and one (0.3%) subject in Study BCM-002 (colon carcinoma in situ). The individual (Subject (b) (6) with peripheral T-cell lymphoma was further evaluated to assess the possibility of oncogenesis due to JCAR017; results were inconsistent with a clonal CAR T-cell proliferative disorder or transgene-induced malignant transformation and insertion site analysis did not reveal integration sites proximal to potentially oncogenic loci.

Among subjects followed in the post-treatment emergent period (N=298), 17 (5.7%) subjects experienced secondary malignancies, including 15 (6.1%) subjects in Study 017001 (five MDS, five basal cell carcinoma, three cutaneous squamous cell carcinoma, one squamous cell carcinoma of the lung, one acute myeloid leukemia, one low-grade appendiceal mucinous neoplasm and one bladder transitional cell carcinoma; one subject experienced three of the above secondary malignancies) and two (9.1%) subjects in Study BCM-002 (two cutaneous squamous cell carcinoma). No secondary malignancies were reported in Study BCM-001 or 017007.

Reviewer comment: The important identified risk of secondary malignancy and insertional mutagenesis will be mitigated through routine pharmacovigilance, targeted questionnaires for secondary malignancies, a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and labeling; a transgene assay service will also be available. This safety concern is labeled in the following section of the USPI:

- *Section 5.8, Warnings and Precautions: Secondary Malignancies*

The proposed PVP is appropriate to mitigate the potential risk of secondary malignancy and insertional mutagenesis.

7.11 Important Missing Information: Impact on pregnancy and lactation

The effect of Breyanzi on pregnancy and lactation is not known.

Reviewer comment: The missing information of impact on pregnancy and lactation of Breyanzi will be mitigated through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, routine pharmacovigilance activities, and labeling. This safety concern is labeled in the following section of the USPI:

- *Section 8, Use in Specific Populations (Section 8.1 Pregnancy, Section 8.2 Lactation, and Section 8.3 Females and Males of Reproductive Potential)*

The proposed PVP is appropriate to mitigate the risk of missing information regarding impact on pregnancy and lactation.

7.12 Important Missing Information: Long-term safety

The sponsor proposes LTFU safety studies for patients who received Breyanzi in clinical trial or postmarketing settings to help address the long-term safety and efficacy of Breyanzi therapy. Section 6, Pharmacovigilance Plan, provides an overview of these studies, which both include 15 years of follow-up as recommended in *Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products* (January 2020) (Section V).

Reviewer comment: The missing information on the long-term safety of Breyanzi will be mitigated through a PMR registry study, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. The proposed PVP is appropriate to collect data on long-term safety.

7.13 Important Missing Information: Safety in pediatrics

The proposed label indication is for treatment of adult patients with R/R large B-cell lymphoma after at least two prior therapies. Subjects < 18 years of age who received JCAR017 in clinical trials will be followed in the LTFU study.

Reviewer comment: The missing information regarding safety in pediatrics will be mitigated through a LTFU safety study for clinical trial subjects and routine pharmacovigilance activities. The proposed PVP is appropriate to mitigate the risk of missing information regarding safety in pediatrics.

7.14 Other Risk of Special Interest: Infusion-related Reactions

IRR were an AESI that occurred in three subjects in Study 017001 and one subject in Study BCM-002 (Grade 1-2). No IRR precluded completion of JCAR017 infusion.

Reviewer comment: This safety concern is addressed in the following sections of the USPI:

- *Section 5.4, Warnings and Precautions: Hypersensitivity*
- *Section 6.1, Clinical Trials Experience*

Risk mitigation through labeling is appropriate. Primary safety endpoints for the PMR registry study will also include Grade ≥ 3 AEs considered related to Breyanzi treatment.

8 DE Conclusions

Based on review of available data, the safety concerns from the Phase 1 and Phase 2 clinical trials warrant a REMS Program with ETASU to mitigate the risks of CRS and NT and a PMR registry study to assess the serious risk of secondary malignancy. In addition, risks of treatment with Breyanzi will be mitigated through risk communication and risk minimization measures as recommended in the USPI, including a Boxed Warning for the risks of CRS and NT, and routine pharmacovigilance activities. The sponsor will also conduct a LTFU safety study for subjects treated with JCAR017 in

clinical trials and will test for JCAR017 transgene on all secondary malignancies where tissue is available in the LFTU study. For the required post-marketing registry study and post-marketing commercial use, transgene testing will be performed for all secondary malignancies of T-cell origin. Patients in the PMR registry will be followed for 15 years.

9 DE Recommendations

Should the product be approved, the sponsor's PVP (Risk Management Plan, Version 1.0, dated September 30, 2019) for Breyanzi, which includes instituting a REMS program with ETASU to ensure that the benefits of the drug outweigh the risks of CRS and NT, and conducting a required post-marketing registry LTFU study (safety related PMR under FDAAA Title IX), and routine pharmacovigilance and AE reporting in accordance with 21 CFR 600.80, is adequate for post-market safety monitoring. The REMS program will require hospital sites to be specially certified and have on-site, immediate (within 2 hours) access to tocilizumab and healthcare provider training about the management of CRS and neurotoxicity. The PMR registry study will further assess the incidence and severity of the serious risk of secondary malignancy as well as other selected AEs, in patients treated with Breyanzi in the post-market setting and will include 15-year follow-up of patients. The content of the REMS program materials should align with the package insert. Please see the final version of the REMS Document, REMS materials, and package insert submitted by the sponsor for the final agreed-upon content and language.

10 References

1. Lee DW, Gardner R, Porter DL et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124(2):188-95.
2. Swerdlow SH, Campo E, Pileri SA et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127(20):2375-90.
3. Schulert G and Grom A. Macrophage activation syndrome and cytokine directed therapies. *Best Pract Res Clin Rheumatol*. 2014;28(2):277-92.
4. Maus MV, Levine BL. Chimeric antigen receptor T-cell therapy for the community oncologist. *Oncologist* 2016;21(5):608-17.

Appendix A: Subjects with Diffuse Large B-cell Lymphoma Experiencing Grade 5 (Death) Treatment-emergent Adverse Events after JCAR017 Treatment, Study 017001*

Subject ID	Age/Sex	Preferred Term and Brief Summary	Study Day of Death	Investigator's Assessment of Relatedness to LDC/JCAR017
Treatment-emergent period				
(b) (6)	82 yr/male	Diffuse alveolar damage ; subject developed fever and chest x-ray showed new small left pleural effusion, patchy bibasilar opacities, and unchanged nodular opacities in right lower lobe on Day 6; developed Grade 3 encephalopathy on Day 8 which improved to Grade 1 on Day 14; developed new oxygen requirement and started on antibiotics on Day 17; Grade 4 neutropenia, Grade 3 thrombocytopenia, and Grade 4 diffuse alveolar damage diagnosed on Day 18; subject had increased work of breathing, placed on non-rebreather mask and became minimally responsive on Day 22; transitioned to do not resuscitate and expired on Day 23; autopsy revealed cause of death to be malignant lymphoma with terminal extensive diffuse alveolar damage, with acute and organizing patterns, lungs with diffuse consolidation and demonstrated hyaline membranes indicative of acute alveolar damage of several days to a few weeks in age	23	Related/Related
(b) (6)	63 yr/male	Pulmonary hemorrhage ; subject experienced Grade 2 agitation, Grade 3 delirium, and Grade 4 CRS on Day 4; experienced Grade 4 acute respiratory failure on Day 6; developed Grade 3 cardiomyopathy of undetermined etiology on Day 10; developed Grade 4 gastrointestinal hemorrhage and Grade 3 thrombocytopenia on Day 22; had prolonged anemia and thrombocytopenia on Day 29; bronchoscopy	33	Related/Related

		confirmed Grade 4 pulmonary hemorrhage with unidentified source of bleeding on Day 31; placed on comfort care on Day 32; died due to pulmonary hemorrhage on Day 33; autopsy revealed widespread high-grade B-cell lymphoma with extensive necrosis in multiple organs, including respiratory system, reticuloendothelial system, and gastrointestinal system which was considered underlying cause of death		
(b) (6)	72 yr/male	Multiple organ dysfunction syndrome ; experienced Grade 2 CRS on Day 4; Grade 4 thrombocytopenia on Day 6; Grade 4 neutropenia on Day 8; disease progression on Day 55; Grade 2 pneumonia on Day 78; Grade 4 sepsis on Day 82; chest x-ray showed pneumomediastinum and subcutaneous emphysema; subject placed on do not resuscitate status on Day 84; died on Day 85 due to multiple organ dysfunction syndrome; autopsy not performed	85	Related/Related
(b) (6)	74 yr/male	Leukoencephalopathy ; Grade 2 leukoencephalopathy diagnosed on Day 43; subject also had ongoing SAEs of blindness and asthenia; autopsy indicated that proximal cause of death was likely bacteremia complicated by therapy associated with neurological disease; investigator assessed leukoencephalopathy as related to fludarabine due to subject's lack of response to dexamethasone and other similar cases of rapid ophthalmic involvement and motor deficit development 30-60 days post-fludarabine	71	Related/Not related
(b) (6)	38 yr/female	Septic shock ; experienced Grade 2 CRS on Day 4; subject diagnosed with Grade 4 septic shock and Grade 4 urinary tract obstruction on Day 5; experienced Grade 3 urinary tract infection and Grade 4 disease progression on Day 6; died on Day 7 due to septic shock; autopsy revealed immediate cause of death was likely sepsis with underlying cause of death of B-cell lymphoma	7	Related/Not related

(b) (6)	51 yr/female	Cardiomyopathy (non-vaso-occlusive cardiomyopathy); cardiomyopathy assessed as possibly caused by JCAR017 due to temporal association; autopsy revealed left neck mass with approximately 50% necrosis and moderate cytotoxic T-cell infiltrate (CD8 cells, but none identified as CAR T transgene), cardiomyopathy with multifocal patchy areas of subendothelial necrosis in left ventricle and interventricular septum, cardiomegaly, and left ventricular hypertrophy	7	Related/Related
(b) (6)	70 yr/female	Progressive multifocal leukoencephalopathy (PML); experienced Grade 2 lethargy, Grade 2 headache, Grade 2 speech disorder, and Grade 3 febrile neutropenia on Day 2; experienced Grade 2 confusional state, Grade 2 mental status changes, Grade 3 dysarthria, and Grade 2 hemiplegia with slurred speech on Day 3; Grade 4 PML diagnosed on Day 4; spinal tap revealed John Cunningham virus by PCR on Day 10; condition worsened and subject died on Day 53; autopsy not performed	53	Not related/Not related
Post-treatment emergent period				
(b) (6)	69 yr/female	Death; subject had disease progression and was re-treated with JCAR017 on Day 287; experienced disease progression again on Day 594/re-treatment Day 29; developed Grade 2 CRS on re-treatment Day 30 while pre-existing atrial fibrillation worsened to Grade 2 and experienced concurrent Grade 3 urinary tract infection; subject hospitalized and then discharged home on re-treatment Day 37; subject began to slur words and expired in ambulance on re-treatment Day 41; cause of death unknown; autopsy not performed	641/Re-treatment Day 41	Not related/Not related
(b) (6)	70 yr/male	Myelodysplastic syndrome; subject experienced disease progression on Day 189 and received subsequent radiotherapy; developed Grade 3 MDS on Day 336; bone	670	Not related/Not related

		marrow biopsy revealed hypercellular marrow, erythroid hyperplasia, dyserythropoiesis, increased megakaryopoiesis, and dysmegakaryopoiesis consistent with Grade 3 therapy related MDS Del7Q and del 7 with no TP53 mutation; biopsy negative for CAR T transgene; died due to MDS on Day 670		
(b) (6)	46 yr/male	Septic shock ; diagnosed with Grade 4 peripheral T-cell lymphoma (PTCL) on Day 30; hospitalized for Grade 4 septic shock with concurrent Grade 4 neutropenia on Day 72; CT chest showed new pulmonary nodules, right renal mass, multiple hypodense hepatic lesions, and splenomegaly; diagnosed with Grade 3 hepatic failure on Day 71; subsequent anti-cancer therapy included bendamustine on Day 74; progressive decline with Grade 3 anemia and neutropenia; transitioned to palliative care and died due to septic shock due to pancytopenia as result of PTCL on Day 79	79	Not related/Not related
(b) (6)	66 yr/female	Progressive multifocal leukoencephalopathy ; subject had received eight prior lines of systemic therapy over 10-year period for treatment of DLBCL; 1-year post-JCAR017 infusion developed acute visual field loss with imaging consistent with occipital stroke, stabilized after anticoagulation; developed difficulty speaking on Day 710 and brain MRI showed occipital lesion on Day 714; brain biopsy positive for John Cunningham virus; condition worsened and died from PML on Day 775; autopsy not performed	775	Related/Related

*Adapted from Table 49 of the ISS and Table 40 of the 3-Month Safety Update Report.

†Subject (b) (6) died after completion of Study 017001.

Appendix B: Subjects with Diffuse Large B-cell Lymphoma Experiencing Grade 5 (Death) Treatment-emergent Adverse Events after JCAR017 Treatment in Supporting Studies, BCM-001, and BCM-002*

Subject ID	Age/Sex	Preferred Term and Brief Summary	Study Day of Death	Investigator's Assessment of Relatedness to LDC/JCAR017
Treatment-emergent period				
BCM-001 (b) (6)	61 yr/male	Respiratory failure ; subject experienced Grade 3 confusional state, depressed level of consciousness, and stupor and Grade 2 CRS on Day 6; CRS worsened to Grade 4 with concurrent Grade 4 depressed level of consciousness and Grade 3 pneumonia on Day 7; diagnosed with Grade 3 MAS and Grade 3 respiratory failure on Day 8; pneumonia worsened and developed Grade 4 respiratory failure on Day 11; diagnosed with Grade 4 Candida sepsis on Day 14; continued decline with Grade 4 pulmonary mycosis and death from respiratory failure on Day 15; autopsy revealed massive pulmonary infiltration and multi-organ abscesses due to <i>Candida krusei</i> sepsis and presence of MAS (not possible to distinguish whether MAS was final event of CRS or induced by sepsis)	15	Not related/Related
BCM-001 (b) (6)	53 yr/male	Candida sepsis ; diagnosed with Grade 4 erythrophagocytosis/MAS on Day 19; experienced Grade 4 Candida sepsis on Day 22; treatment stopped, and palliative care initiated on Day 35; died of worsening Candida sepsis and progressive disease on Day 43; autopsy showed extensively advanced malignancy; cause of death considered to be underlying disease, complicated by bone marrow suppression	43	Related/Related

BCM-001 (b) (6)	56 yr/female	Multiple organ dysfunction syndrome; experienced disease progression on Day 17 and received subsequent anticancer therapy, including external beam radiation; experienced Grade 4 thrombocytopenia on Day 32 and Grade 2 leukopenia on Day 35; subject transferred to hospital for palliative care and experienced rapidly progressive liver disorder, anuria, and hypoxia on Day 52; died on Day 52	52	Not related/Not related
BCM-002 (b) (6)	67 yr/female	Staphylococcal sepsis; subject hospitalized for Grade 2 CRS on Day 14; experienced Grade 4 thrombocytopenia on Day 16; developed Grade 4 encephalopathy, Grade 4 peripheral motor neuropathy, Grade 2 confusional state, and Grade 1 mental status changes on Day 19; blood and urine cultures positive for <i>Staph aureus</i> and diagnosed with Grade 4 <i>Staph aureus</i> sepsis on Day 20; developed Grade 3 urinary tract infection on Day 22; family decided to pursue comfort care; died of <i>Staph aureus</i> sepsis on Day 25; autopsy not performed	25	Related/Not related
BCM-002 (b) (6)	73 yr/male	Pneumonia; subject experienced prolonged cytopenia (Grade 4 neutropenia and thrombocytopenia) on Day 29; Grade 2 intracranial hemorrhage and hospitalized on Day 30 (improved to Grade 1 on Day 36); experienced Grade 3 pneumonia on Day 40 and re-hospitalized; died of pneumonia on Day 45	45	Not related/Not related
Post-treatment-emergent period				
BCM-002- (b) (6)	65 yr/male	Sepsis; subject diagnosed with Grade 1 colon adenoma and Grade 3 colon cancer stage 0 on Day 36 (no record of colon cancer sample being received for testing with JCAR017 transgene assay); developed Grade 3 mental status changes and hospitalized on Day 75; Grade 2 acute	95	Related/Not related

		kidney injury and Grade 4 sepsis diagnosed on Day 79 with concurrent Grade 4 thrombocytopenia and hyperkalemia; blood cultures positive for Candida on unknown date; diagnosed with Grade 3 pneumonia on Day 90 with CT chest suggesting aspiration or bronchopneumonia and showing multiple lung nodules suspicious for fungal lung infection; status declined and transferred to hospice; died due to sepsis on Day 95; unknown if autopsy performed		
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*Adapted from Table 54 of the ISS and Table 40 of the 3-Month Safety Update Report. No deaths were reported in Study 017007.