BLA Clinical Review Memorandum

Application Type	Original Application
STN	125646
CBER Received Date	February 2, 2017
PDUFA Goal Date	October 3, 2017
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Maura O'Leary, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Donna Przepiorka, MD, PhD Bindu George, MD Marc Theoret, MD
Applicant	Novartis
Established Name	Tisagenlecleucel (CTL019)
(Proposed) Trade Name	KYMRIAH™
Pharmacologic Class	CD19-directed genetically-modified autologous T-cell immunotherapy
Formulation(s), including Adjuvants, etc.	Cryopreserved injection containing Plasma-Lyte A, Dextrose in sodium chloride (NaCl), Dextran 40 in Dextrose, Human Serum Albumin (HSA), and Cryoserv® dimethylsulfoxide (DMSO)
Dosage Form(s) and Route(s) of Administration	A single dose of KYMRIAH contains 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 0.1 to 2.5 x 10^8 CAR-positive viable T cells for patients more than 50 kg, suspended in one or more patient-specific infusion bag(s) for intravenous use
Dosing Regimen	Once 2 to 14 days after lymphodepleting chemotherapy
Proposed Indication(s) and Intended Population(s)	Kymriah is a genetically modified autologous immunocellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)
Orphan Designated (Yes/No)	Yes

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Glossary

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocte Count
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/SGPT
AML	Acute Myelogenous Leukwimia
BLA	Biologics License Application
BOR	Best Overall Response Rate
CAR	Chimeric Antigen Receptor
CBC	Complete Blood Count
CHF	Congestive Heart Failure
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
Cr	Creatinine
CR	Complete Remission
CRh	Complete Remission with partial hematologic recovery
CRi	Complete Remeission with incomplete hematologic recovery
CSF	Cerebrospinal Fluid
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DIC	Disseminated Intravascular Coagulation
SDOR	Duration of Response
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiography
EFS	Event-Free Survival
EMA	European Medicines Agency
EOT	End of Treatment
ETASU	Elements to Assure Safe Use
EVI1	Ecotropic Viral Integration Site 1
FAS	Full Analysis Set
FDA	Food and Drug Administration
F/U	Follow-up
GMP	Good Manufacturing Practice
HAMA	Human Anti-Mouse Antibodies
HCP	Healthcare Providers
HHV-6	Human Herpes Virus-6

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GMP	Good Manufacturing Practice
HAMA	Human Anti-Mouse Antibodies
HCP	Healthcare Providers
HHV-6	Human Herpes Virus-6
HR	Hazard Ratio
HSV	Herpes Simplex Virus
IA	Interim Analysis

IMM	Irreversible Morbidity or Mortality
IND	Investigational New Drug Application
IRC	Independent Review Committee
ITT	Intent-To-Treat
IV	Intravenous
LP	Lumbar Puncture
LTFU	Long-Term Followup
MedDRA	Medical Dictionary for Regulatory Activities
MDS1	Myelodysplasia Syndrome Protein 1
MHC	Major Histocompatability Complex
MLV	Murine Leukemia Virus
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MUGA	Multiple Uptake Gated Acquistion
N	Number of Subjects
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NR	No Response
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall Remission Rate
OS	Overall Survival
Ph+	Philadelphia Chromosome Postive
PI	Package Insert
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient Reported Outcomes
qPCR	Quantitative Polymerase Chain Reaction
PML	Progressive Multifocal Leukoencephalopathy
Pre	Sampling Done Before Injection
RCR	Replication-Competent Retrovirus
REMS	Risk Evaluation and Mitigation Strategy
RFS	Relapse-Free Survival
SAE	Serious Adverse Event
ScFv	Single-Chain Variable Fragment
SD	Stable Disease
SIN	Self-Inactivating
SPA	Special Protocol Assessment
TCR	T-cell Receptor
TKI	Tyrosine Kinase inhibitor
UNK	Unknown
U.S.	United States
VCN	Vector Copy Number
WBC	White Blood Count

1. EXECUTIVE SUMMARY

Tisagenlecleucel is comprised of genetically-modified antigen-specific autologous T cells reprogrammed to target cells that express CD19, an antigen on the surface of normal B cells and tumors derived from B cells. The tisagenlecleucel chimeric antigen receptor (CAR) protein consists of an extracellular portion that has a murine anti-CD19 single chain antibody fragment (scFv) and an intracellular portion that contains T-cell signaling (CD3-ζ) and co-stimulatory (4-1BB) domains. These intracellular domains play critical roles in tisagenlecleucel's functions, including T-cell activation, persistence in vivo and anti-tumor activity.

The Applicant's proposed indication was for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL). The Applicant submitted one trial (CCTL019B2202) in support of this proposed indication. This study was conducted under a Special Protocol Assessment agreement and served as the sole source of efficacy and safety data in this review.

CCTL019B2202 (B2202) is a multicenter, open-label, single-arm trial to determine the efficacy and safety of CTL019 in pediatric and young adult patients with R/R B-cell ALL. The pre-specified primary endpoint in B2202 was overall remission rate (ORR) during the 3 months after tisagenlecleucel administration; ORR included complete remission (CR) and CR with incomplete hematologic recovery (CRi), as determined by an independent review committee (IRC). A key secondary endpoint was achievement of minimal residual disease (MRD)-negativity in the responders. The efficacy analysis population is limited to the 63 patients treated with products from the Morris Plains manufacturing site, since there was insufficient information to confirm that products manufactured at other sites were comparable. The independent review committee (IRC) identified ORR in 52 of 63 patients (82.5%; 95% CI 70.9, 91.0). Responses included 40 CR and 12 CRi. All 52 responders were MRD-negative. The median follow-up is 4.8 months (range 1.2-14.1 months); only 11 responders relapsed within the follow-up period, and the median duration of remission was not reached.

ORR has not been considered an optimal endpoint for a regular approval for R/R ALL. FDA has used durable CR for determination of clinical benefit on the basis of recovery of adequate blood counts to protect against infection and avoidance of transfusions. For the 63 patients in the efficacy analysis population, the CR rate was 63% (95% CI, 50, 75), and all patients in CR were MRD negative. With a median follow-up of 4.8 months, the median duration of CR was not reached.

The safety assessment of tisagenlecleucel included both clinical and theoretical considerations. B2202 was the primary source of safety data. The adverse reactions of interest were cytokine release syndrome (CRS) (Grade 3+4 [49%]), neurologic events (Grade 3 [18%]), febrile neutropenia (Grade 3+4 [38%]), prolonged cytopenias (Grade 3+4 [37%]), and infections (Grade 3+4 [27%]). The theoretical concerns include an increased risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional mutagenesis. There were no events of RCR infection or insertional mutagenesis reported in the BLA. Persistence of tisagenlecleucel *in vivo* up to at least 366 days was documented without late adverse reactions other than prolonged hypogammaglobulinemia resulting from the off-tumor, on-target elimination of normal B cells.

A major consideration in the review of this product is the restriction of the proposed indication to a pediatric and young adult population. There was insufficient information in the BLA to confirm safety or efficacy of the recommended dose in older adults with ALL.

During conduct of the B2202, life-threatening and fatal adverse reactions caused by tisagenlecleucel 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, including a boxed warning for CRS and neurotoxicity, and a Risk Evaluation and Mitigation Strategy (REMS). FDA determined in consultation with the OBE and CDER DRISK that the Communication Plan as proposed by the Applicant would not be sufficient; instead, a REMS with elements to assure safe use (ETASU) was the appropriate approach. The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies with emphasis on recognition and treatment of CRS and neurotoxicity (FDA Draft Guidance, September 2016).

Long-term safety after treatment with tisagenlecleucel remains a concern. Due to the lack of long-term safety data in the BLA, additional study postmarketing is warranted. As a postmarketing requirement (PMR), the applicant agreed to conduct an observational study (CCTL019B2401) that will collect safety information for patients treated with 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 evaluate for RCR or tisagenlecleucel persistence is planned as part of this study.

The Advisory Committee (CDER's Oncologic Drugs Advisory Committee) met on July 12, 2017. The committee voted 10 to 0 that tisagenlecleucel had a favorable benefit-risk profile for the treatment of pediatric and young adults (age 3-25) with relapsed (second or later) or refractory (failed to achieve an initial remission to initial induction or reinduction chemotherapy) B-cell precursor ALL. The discussion focused on four issues, as follows:

- CMC: Discussion of control of product quality for tisagenlecleucel with respect to identity, safety, purity and potency, including design of the CAR construct and viral vector, and assessment of CAR expression and T-cell activity
- CMC: Discussion of the potential safety concerns with tisagenlecleucel and other retrovirus-based gene therapy products include generation of replication-competent retrovirus (RCR) and insertional mutagenesis.
- Clinical: Discussion of strategies for mitigation of short-term safety risks, including CRS, on the B2202 trial and as anticipated for the commercial setting.
- Clinical: Discussion of the planned 15-year follow-up centered on the B2401 postmarketing observational trial.

Tisagenlecleucel has orphan designation, so this BLA is exempt from the requirements of PREA. The applicant submitted a proposal for pediatric studies request for the B2202, and a Written Request was issued under the Best Pharmaceutical for Children's Act (BPCA). The results of B2202 submitted in this BLA fulfill the criteria in the Written Request.

Clinical Reviewer's Recommendation on Regulatory Action:

Following review of the BLA clinical efficacy (63 patients treated with tisagenlecleucel manufactured in Morris Plains, New Jersey [MP]) and safety data (68 patients treated with tisagenlecleucel manufactured in MP and at the Fraunhofer Institute, Germany), and considering the available therapies for R/R ALL, as well as the discussion at the ODAC meeting, the clinical review team recommends issuing regular approval (21 CFR 601.4 (a)) for tisagenlecleucel. While the safety risks both known and theoretical are substantial, the achievement of a CR in 63%, all of which were MRD-negative, provides a favorable risk/benefit profile for this population of highly-resistant pediatric and young adult ALL, and supports approval for the dose of 0.2-5 x 10^6/kg for patients less than or equal to 50 kg or 0.1-2.5 x 10^8 for patients over 50 kg as demonstrated in Study B2202.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Of the 107 patients who signed an informed consent, 88 were enrolled. Sixty-eight patients received tisagenlecleucel with products manufactured at Morris Plains (MP), New Jersey (n=63) and Fraunhofer Institute, Germany (n=5). The safety analysis population included all 68 patients treated, and the efficacy analysis population included the 63 patients treated with product from the Morris Plains site.

Table 1 shows the baseline demographics for all patients enrolled, patients in the safety analysis set and patients in the efficacy analysis set. The numbers of patients in various demographic subgroups are too small to allow an accurate assessment for differences in safety or efficacy by subgroup.

Table 1: Demographics of the Enrolled Set, Safety Analysis Set, and Efficacy Analysis Set

Category	Subcategory	Enrolled Set N=88	Safety Analysis Set N=68	Efficacy Analysis Set* N=63
Sex	**Male** **Female**	**48 (55%)** **40 (45%)**	**38 (56%)** **30 (44%)**	**35 (56%)** **28 (44%)**
Age	**Mean (SD)** **Median** **Min-Max**	**12.1 (5.4) yrs.+** **11.5 yrs.** **3-27 yrs.**	**12.2 (5.3) yrs.** **12 yrs.** **3-23 yrs.**	**12 (5.4) yrs.** **12 yrs.** **3-23 yrs.**
Age category	**2 to < 12 years** **12 to < 17 years** **≥17 years**	**44 (50%)** **22 (25%)** **22 (25%)**	**31 (49%)** **17 (27%)** **15 (24%)**	**33 (49%)** **19 (28%)** **16 (24%)**
Race	**White** **Asian** **Other**	**65 (74%)** **10 (11%)** **13 (15%)**	**51 (75%)** **6 (9%)** **11 (16%)**	**46 (73%)** **6 (10%)** **11 (17%)**
Ethnicity	**Hispanic** **Other**	**17 (19%)** **71 (81%)**	**14 (21%)** **54 (79%)**	**14 (22%)** **49 (78%)**

*Product manufactured in Morris Plains, New Jersey; +yrs. = years
Source: FDA Stat Reviewer; ADSL JReview

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia can be of B- or T-cell origin. B-cell precursor ALL in pediatric and young adult patients is characterized by a common antigen on the membrane of the cell in the majority of cases, not only at initial diagnosis, but at relapse. This antigen is CD19. Approximately 80-85% of pediatric ALL diagnosis are B-cell precursor in origin and CD19 positive (CD19+).

CD19

Expression of CD19 is restricted to B lineage cells and is not expressed by pluripotent blood stem cells (Uckun, 1988). Since CD19 presence on normal cells is limited to B- cells, the effect of an anti-CD19 agent would primarily affect B-cell function which is amenable to replacement with intravenous immune globulin. CD19 is expressed by most B-cell malignancies in particular B-cell precursor ALL (Uckun, 1988; Scheuermann, 1995; Schwonzen, 1993). This made CD19 a natural target for immunotherapy (Uckun, 1988). The strategy with tisagenlecleucel was to produce genetically engineered chimeric antigen receptor (CAR) T cells transfected with chimeric receptor genes to combine the effector functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner. The target was CD19 on the surface of the B-cell precursor blasts.

Pediatric and Young Adult B-cell Precursor Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) occurs in children and adults. Each year 3100 new cases are reported in children and adolescents. 60% of ALL is diagnosed in patients less than 20 years of age. ALL comprises 25% of all cancer diagnoses in children less than 15 years old and 19% of all cancers in patients less than 20 years old (Hunger, 2013). The peak incidence is at age 2 -3 years. The 5-year survival rate in children is 90% using intensive chemotherapy over 2 to 3 years. There are multiple prognostic indicators such as initial white blood count (WBC), age, cytogenetics, ethnicity, race, sex, gene polymorphisms in drug metabolic pathways, genetic alterations, and rapidity of response to induction therapy as measured by minimal residual disease (MRD).

Survival after relapse is dependent on the timing of the relapse and the type of relapse. In a review of the survival after relapse in results for children and adolescents diagnosed with ALL and treated on Children's Oncology Group protocols from 1988 through 2002, the authors confirmed the link between survival with timing and types of relapse. The total number of patients was 9585 with *de novo* ALL and 1961 patients relapsed (20%) (Table 2(Nguyen, 2008)). The population was 86% B-cell precursor ALL and 14% T-cell ALL. Risk factors for decreased survival after relapse included: time from initial diagnosis to relapse and site of relapse. Survival rates (5-year) for relapse in this review (Nguyen, 2008) of COG data for relapse after initial therapy demonstrated: early bone marrow relapse (less than 18 months from diagnosis) was 11%, in all BM relapses the overall survival was 24%; for early marrow relapse with concurrent extramedullary relapse, survival was 12%, overall concurrent relapses survival was 39%. With more aggressive therapies for front-line treatment, salvage therapy has become less effective (Ko, 2010; Pui, 2013). The only potential cure for relapsed systemic pediatric ALL is allogeneic stem cell transplantation (HSCT). Survival after HSCT for relapsed

ALL is improved if the patient is transplanted in a minimal residual disease negative remission (Pulsipher, 2014).

The majority of the 1400 ALL deaths a year in the U.S. are in adults. However, relapsed ALL remains a leading cause of cancer deaths in children in the U.S. (Raetz, 2012; Carroll, 2016).

Table 2: Survival Based on Time to ALL Relapse and Site of ALL Relapse

5-year survival Post-relapse	Relapse site			
	Isolated BM		Concurrent BM+ extramedullary	
Time to Relapse	n	OS % (s.e.)	n	OS % (s.e.)
Early	412	11.5 (1.9)	86	11.6 (4.9)
Intermediate	324	18.4 3.1)	54	39.8 (9.3)
Late	387	43.5 (5.2)	124	60.3 (8.3)
Overall	1123	24.1 (2.1)	264	39.4 (5.0)

Adapted from Nguyen et al, 2008; s.e.: standard error

Reviewer Comment: Pediatric B-cell precursor ALL has been the success story for pediatric oncology. Unfortunately, refractory disease and relapses still occur. With more aggressive therapy after successful induction therapy, the use of conventional agents with initial relapse has been less successful, particularly if the relapse occurs while on therapy. The incidence of refractory disease has decreased but in the less than 1% who has refractory disease to initial therapies, the outcome is dismal unless a MRD negative remission can be obtained to allow for a stem cell transplant (HSCT). The prognosis for relapsed pediatric ALL in the absence of a successful HSCT is dismal. Regardless of when the relapse occurs, relapses continue to happen with shortened periods of remission. Even transplant has limited success rates, so the potential to treat multiply relapsed patients successfully with sustained remissions would be a therapeutic advance.

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

2.2.1 Treatment of Refractory Disease

Patients with primary refractory and chemorefractory B-cell precursor ALL have an extremely poor prognosis. These patients are refractory to the best available combination therapies and therefore unable to proceed for HSCT which has the potential to be curative in MRD-negative CR for these patients. Usual treatment includes combinations of the single agents in Table 3. Complete remission rates with salvage therapy after second or subsequent BM relapse is 40% (Raetz, 2012). Blinatumomab and clofarabine are both approved for refractory ALL in pediatric and young adult patients with R/R ALL as single agents as noted below. Information on the efficacy of vincristine sulfate liposome injection is included in Table 4 because there were adult patients 18-23 years of age treated on the B2202 study.

2.2.2 Treatment of Relapsed Disease

Table 3: FDA-Approved Therapies for ALL

Agent	Indication
Asparaginase	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL)
Blinatumomab	Indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
Clofarabine	Indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens
Cyclophosphamide	Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often suscept ble to cyclophosphamide treatment: acute lymphoblastic (stem-cell) leukemia in children.
Cytarabine	Useful in treatment of general ALL
Dasatinib	Adults with Ph+ ALL with resistance or intolerance to prior therapy
Daunorubicin	Indication in combination with other approved anticancer drugs is indicated for remission induction in acute lymphocytic leukemia of children and adults.
Doxorubicin	Indicated to induce remission in general ALL
Erwinia Asparaginase	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) and hypersensitivity to native forms of L- asparaginase.
Imatinib	Adult patients with newly diagnosed Philadelphia chromosome positive ALL (Ph+ALL) Pediatric patients with newly diagnosed PH+ ALL in combination with chemotherapy
Mercaptopurine	For maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen
Methotrexate	Used in maintenance therapy in combination with other chemotherapeutic agents.
Pegasparaginase	Indicated as a component of a multi-agent chemotherapeutic regimen for first line treatment of patients with acute lymphoblastic leukemia (ALL), and ALL with hypersensitivity to asparaginase
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Teniposide	In combination with other approved anticancer agents, is indicated for induction therapy in patients with refractory childhood acute lymphoblastic leukemia.
Vincristine	Indicated in acute leukemia.
Vincristine sulfate liposome injection	Treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.

Date: 7/15/2017

Table 4: Efficacy of FDA-Approved Single-Agent Therapy For Relapsed/Refractory Acute Lymphoblastic Leukemia In Pediatric And Young Adult Patients

FDA-Approved Products	Approval Year	Population	Efficacy Outcome
Clofarabine	2004 (accelerated approval)	N=61 R/R ALL Median Age 12 R/R 2 or more therapies 57% prior-HSCT Median treatment with clofarabine: 1 cycle (1-5 cycles)	CR% 11.5% (4.7, 22.2); CRp%: 8.2%; DOR: 10.7 weeks (2.5 months) censored at transplant
Vincristine sulfate liposome	2012 (accelerated	N=65 R/R ALL 45% under 30	Approval in Ph chromosome negative adult R/R ALL65; relapsed or refractory after 2

FDA-Approved Products	Approval Year	Population	Efficacy Outcome
injection	approval)	R/R after 2 or more therapies 51% 3 or more prior therapies 48% post-HSCT Received at least one dose of vincristine sulfate liposome injection	or more therapies; 48% prior transplant; 45% under 30. CR 3 (4.6%); CRi 7 (10.8%); CR+CRi 10 (15.4%) DOR: From CR/CRi to date of last assessment: 28 days (1 month); CR/CRi to date of relapse, death, new therapy 56 days (2 months)
Blinatumomab	2014	N=70; median age 8 (7 months-17 years; 57% prior HSCT; Median treatment with blinatumomab: 1 cycle (1-5)	CR 12 (17%), CRh 11 (16%), CR/CRh 23 (33%); MRD 6/12 CR; 4/11 CRh; 10/23 CR/CRh DOR: CR/CRh: 6 months (median)

CR: complete remission; CRp: CR without platelet recovery; PR: partial response; CRh: CR with partial hematologic recovery; CRi: CR with incomplete hematologic recovery DOR: duration of response; MRD: minimal residual disease (10^{-4}) Source: USPI for blinatumomab, vincristine sulfate liposome injection, clofarabine

Reviewer Comment: The published literature and the treatment results for available FDA-approved therapies for relapsed/refractory B-cell precursor ALL do not provide sustained remissions in the R/R B-cell precursor ALL population. In addition, the chance of a remission after second or subsequent relapse is 40% with combination therapy with available chemotherapy agents. There is clearly an unmet need for the treatment of this population.

2.3 Safety and Efficacy of Pharmacologically Related Products

Tisagenlecleucel is a first-in-class anti-CD19 CAR T cell for therapeutic use thus there are no efficacy results for comparison in this product class. See Section 2.1 for the efficacy results for blinatumomab, the only available product in a related product class.

Pharmacologically-related products include those that activate T cells *in vivo*, target B cells, alter the cells' genome, or which contain similar reactive excipients or foreign proteins. There are known safety issues for pharmacologically-related products that are related to the activation of T cells *in vivo*. These may include elimination of normal B cells, insertional mutagenesis, and allergic reactions to excipients such as DMSO or to foreign protein components.

Therapies that activate T cells have been under study for many years. Examples include:

- Allogeneic hematopoietic stem cell transplantation and donor lymphocyte infusions to stimulate a graft versus leukemia reaction in myeloid leukemias
- Tumor infiltrating lymphocytes as a treatment for melanoma
- Cytotoxic T lymphocytes as antiviral agents and for treatment of Epstein-Barr related (EBV) related malignancies
- Genetically modified T cells (lentiviral or gammaretroviral vectors) to produce a chimeric antigen receptor that targets antigens on malignant cells
- Activating anti-CD3 antibodies such as muromonab-CD3
- Bispecific antibodies or novel constructs that retarget CD3+ T cells to an alternative antigen, such as blinatumomab

The approved related drug, blinatumomab, carries a boxed warning for cytokine release syndrome and neurological toxicities.

Cytokine release syndrome (CRS), a systemic reaction that coincides with immune activation and T-cell expansion, is an adverse event typical of these products. Characteristics include fever, fatigue, hypotension/tachycardia, nausea, capillary leak, cardiac/renal/hepatic dysfunction. Inflammatory cytokines are elevated, particularly of note interleukin-6 (IL-6). Treatment and assessments of the extent of CRS have evolved with the field. Treatment is directed at signs and symptoms. In addition, investigators have reported that the anti-IL-6 receptor inhibitor tocilizumab moderated the course of CRS with rapid reversal of symptoms.

In addition, a pattern of neurologic dysfunction has also been described with these products (e.g. blinatumomab). It is characterized by confusion, delirium, expressive aphasia, obtundation, myoclonus, and seizures. More recently, reports of cerebral edema have been reported with CD19 CAR T-cell treatments.

Therapies that target B cells include numerous monoclonal antibodies such as rituximab. These products have an on-target, off-tumor toxicity, the destruction of normal B cells, which necessitates that recipients receive regular infusion of immune globulin. Even with this mitigation, patients may be at increased risk for infection (Bonifant 2016). There are warnings in product labeling about long-term hypogammaglobulinemia and recommendations regarding immunizations.

For products that have been genetically-modified by retroviral transduction, there are additional considerations related to possible generation of second malignancies. Early in the development of gene therapies, in the setting of modification of hematopoietic stem cells, there were reports of insertional oncogenesis with retrovirus transduction in patients receiving a genetically modified (retroviral vector) stem cells. HSCT was followed by the development of T-cell leukemia in recipients of HSCT with gene-modified stem cells for severe combined immunodeficiency and chronic granulomatous disease. These were reported up to 15 years after the procedure. CAR T-cell products can and do persist for years after treatment. This is associated with the design of the product It confers a theoretical increase in the risk of a second malignancy, and insertional mutagenesis.

Anaphylaxis may be a risk due to allergenic excipients such as DMSO or when a biologic is derived from a murine source. There is also a risk from the other foreign components in the infusion. Approved drugs or biologics for intravenous use which contain DMSO (such as Hemacord) carry warnings for the risk of infusion-related reactions that can be severe or fatal.

Tisagenlecleucel is an autologous product, but theoretically there could also be a risk of graft-versus-host disease, especially in patients with residual donor lymphocytes from prior failed HSCT, since the donor cells in the recipient are in the apheresis collection for manufacturing.

Reviewer Comment: The experience with tisagenlecleucel is first reported with this BLA. Reviews published on the toxicity of activated T-cell therapy provide an insight to the risks and management of the short-term toxicities such as CRS and neurotoxicity. Long-term risks associated with secondary malignancy remain theoretical, but in a heavily pretreated cancer patient may augment a risk that already exists due to prior exposure to carcinogenic cytotoxic agents. Long-term follow-up programs that document the incidence of second malignancy,

comparisons with known and established risks for the patients' baseline therapies, and evaluation of tumor tissue for the vector will be critical to delineate an accurate oncogenic risk profile for these products. These short-term and long-term issues should be addressed in the label, the REMS with ETASU, and a required postmarketing observational study.

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

This is a first-in class product and there is no previous human experience with this CAR product, tisagenlecleucel. (See Section 2.3)

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

Table 5: Regulatory Activity

Date	Milestone and Comments
4/22/2013	PreIND Meeting • Two trials discussed: Phase 2 for pediatric R/R ALL and Phase 2 for R/R chronic lymphocytic leukemia • Revisions to both protocol recommended • Lack of comparability testing for CART19 from the University of Pennsylvania • Discussion of regulatory pathway
10/25/2014	PreIND Meeting • CMC focus on product comparability • Discussion of vector characteristics • Discussion: replication competent retrovirus (RCR) testing
3/03/2014	Special Protocol Assessment (SPA) • Under PS002314 preIND • Protocol revisions for concurrence o Primary efficacy analysis by IRC o Agreed to FDA requests for CD19+ confirmation, added CSF evaluation to CR/CRi assessment, added treatment algorithm for CRS
9/23/2014	IND 16130 submission • CCTL019B2202: single arm, open label, multi-institutional trial of tisagenlecleucel in pediatric and young adult R/R ALL o Modification for safety and dose adjustment to 2 - 5 x 10^6 CTL019 transduced cells/kg for patients less than 50 kg and a dose of 2.5 x 10^8 CTL019 cells if greater than or equal to 50 kg based on updated safety information from cross-referenced IND.
9/23/2014	Rare Disease Designation
1/31/2014	Orphan Designation: Acute Lymphoblastic Leukemia
4/08/2015	First patient enrolled into Study CCTL019B2202
2/29/2016	Breakthrough Therapy Designation • 34 enrolled patients; response data on 23 (2/25/16) • 82% ORR (CR + CRi [n=19]), MRD negative (n=19) • Two early deaths, progressive disease, intracranial hemorrhage • CRS Grade 3/4 is 50%

11/21/2016	Pre-BLA Meeting • Revision of CMC submission to BLA to conform to FDA guidelines • Applicant to submit vector information as separate section • Within 30 days of filing complete efficacy data with six months of duration of response follow-up within 30 days of filing and complete six months of safety within 60 days of filing • Discussion of comparability studies planned for the commercial tisagenlecleucel
11/23/2016	Efficacy Assessment: Data Cut-off
12/01/2016	Written Request issued under IND 16130
12/16/2016	CCTL019B2202 Interim Analysis with 6 months follow-up
1/19/2017	Deaths and SAEs in ongoing studies cut-off
2/02/2017	BLA 125646 submission
3/15/2017	Office of Orphan Drug Products: request for Rare Pediatric Disease Designation Granted.
3/28/2017	Filing Letter • Request for protocol(s) for postmarketing registry and follow-up for patients exposed to a lentiviral vector.
7/12/2017	Oncologic Drugs Advisory Committee Meeting • See Section 5.4.1 for summary of discussion

Table 6: BLA Information Requests (IR) from Clinical, CMC, and Statistical Reviewers

125646 amendments				
Number	Request	Submitted	Type	Notes
1	2/7/2017	2/7/2017	Clinical	correction of study entries
2		2/23/2017	Clinical	First interpretable results B2202 with 6 months follow-up analysis
3	2/15/2017	2/28/2017	CMC	Site contact information, production schedules for CMC inspections
4	11/21/2016	3/2/2017	Clinical	30-day submission update of all datasets B2202 for 6 months safety and efficacy; update safety datasets for B2102J, A2201 and efficacy B2102J
5	2/27/2017	3/10/2017	Clinical	Independent review committee case report forms
6	2/24/2017	3/14/2017	CMC	SOPs
7	3/9/2017	3/15/2017	Statistics	Clarification of analysis
8	3/3/2017	3/15/2017	CMC	Dynabeads, MOI determination, vector container
9	2/27/2017	3/17/2017	Statistics	Define file
10	2/27/2017	3/30/2017	CMC	Feb 27 IR: DMPQ about MP

125646 amendments				
Number	Request	Submitted	Type	Notes
11		3/31/2017	Clinical	60 day safety update; financial disclosures, draft label,
12		4/3/2017	CMC	(b) (4) correction: dose 1e6 CAR+cells/kg; 0.3e9 total viable cells/dose
13	3/7/2017 3/9/2017 3/24/2017	4/7/2017	CMC	Vector CCI & E/L, DMPQ (b) (4), DMPQ (b) (4) bioburden val
14	3/23/2017	4/7/2017	CMC	March 23 IR: analytical methods changes: flow, cell count, mycoplasma; FMO
15		4/14/2017	CMC	DBSQC: mycoplasma testing
16		4/19/2017	Clinical	Advanced training for new treatment sites
17	4/17/2017	4/26/2017	Clinical	Outcome preinfusion; relapses Post-tisagenlecleucel
18		4/27/2017	Administrative	Exemption from drug supply chain security act (DSCSA)
19	4/26/2017	4/28/2017	Clinical	Cellular kinetics files
20	4/6/2017 4/7/2017 4/17/2017	5/1/2017	CMC	DBSQC, vector tables, T-cell subsets
21	3/29/2017 4/21/2017 4/27/2017	5/2/2017	Clinical/ Statistics	Multiple IR requests
22			NONE	
23	4/24/2017	5/5/2017	CMC	Validation of analytical procedures noncompendial (DMSO)
24	3/13/2017	5/10/2017	Administrative	DSCSA
25			NONE	
26	5/2/2017	5/12/2017	CMC	Registry study sample collection,
27	5/2/2017 5/5/2017	5/12/2017	Clinical	DRISK Tocilizumab/Siltuximab PK Clinical Efficacy evaluation
28		5/19/2017	Administrative	Tocilizumab efficacy supplement authorization
29	5/23/2017	5/25/2017	Clinical	CRS
30	5/2/2017 5/4/2017 5/10/2017	5/30/2017	CMC	May 2, 4, 10 IRs: mycoplasma, MOI determination trends, flow comparison and files
31		6/6/2017	Administrative	USAN: tisagenlecleucel
32		6/16/2017	CMC	Mycoplasma, dynabeads

125646 amendments				
Number	Request	Submitted	Type	Notes
				shipping, MOI Val report, shipping qualification, PV
33		6/16/2017	Clinical	DSCSA
34	6/16/2017	6/21/2017	CMC	Lot release info for PV lots
35	6/1/2017 6/6/2017 6/9/2017 6/14/2017	6/22/2017	Clinical	Multiple IR requests; PK, PD
36			NONE	
37	6/9/2017	6/29/2017	Clinical	Reviewable SDTM and ADAM datasets
38	6/20/2017 6/20/2017 6/23/2017 6/27/2017	6/30/2017	Clinical	CD4/CD8 ratio; Tocilizumab, and CRS, CRS and neuro, LTFU
39	6/16/2017 6/22/2107 6/26/2017	7/7/2017	CMC	IR
40	6/20/2017	7/7/2017	Clinical	CRS
41	6/27/2017	7/10/2017	OBE, Clinical	Response to REMS notification letter
42			NONE	
43	7/5/2017 7/5/2017	7/12/2017	Clinical	IR Cytokine Release, and Site Training Materials
44	7/6/2017 5/15-25/2017	7/18/2017	CMC	IR Quality, response to inspections at (b) (4)
45	7/6/2017 7/7/2017 7/13/2017	7/25/2017	CMC	IR vector testing, cell bank qualification, other manufacturing specifications
46	7/21/2017	7/25/2017	CMC	IR manufacturing specifications
47	7/17/2017 7/19/2017 7/21/2017 7/24/2017	8/1/2017	Clinical	IR: renal injury, PMR registry study, B2205J manufacturing sites, Metrics for site training
48	5/15-25/2017 7/17/2017	8/2/2017	CMC	IR vector information
49	7/26/2017	8/3/2017	Clinical	IR revised Medication Guide
50	7/28/2017	8/4/2017	CMC	IR additional information on manufacturing
51	7/28/2017	8/10/2017	CMC	IR manufacturing
52	8/4/2017	8/11/2017	CMC	Container Label

No amendment submissions received after August 12, 2017 were considered by the Clinical Review Team for this review.

2.6 Other Relevant Background Information

For the purposes of regulatory decision-making for products for treatment of relapsed or refractory acute leukemia, durable complete response (CR) may considered an established endpoint denoting clinical benefit for regular approval (FDA Guidance for Industry, 2007), as was used in the original approval of inotuzumab ozogamicin. CR with partial hematological recovery (CRh) that is durable may also be considered a clinical benefit for regular approval, especially when supported by data showing transfusion-independence, as was used in the original approval of enasidenib. CR with incomplete hematological recovery (CRi) may reflect some degree of the activity of a therapy and may be useful for developmental decision-making in early phase clinical trials, but the available data have not established that CRi itself is a clinical benefit.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review. However, the supplemental efficacy information one month into the process which was agreed upon in the pre-BLA meeting, delayed the efficacy analysis.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch Monitoring (BIMO) inspections were issued for two foreign and four domestic clinical study sites that participated in the conduct of Study CCTL019B2202 under IND 16130. All of the inspections were completed and the Establishment Inspection Reports (EIRs) were received and reviewed. A Form FDA 483 was issued to three of the four domestic study sites, but the findings did not significantly impact the data submitted in the BLA. There were a total of twenty-five study centers across 11 countries that participated in the conduct of the study, and enrolled a combined total of 88 patients. The six study sites inspected enrolled a total of 26 patients, which represented approximately 29.5 percent of all patients (N=88) enrolled in the CCTL019B2202 study.

The table below summarizes the inspection results.

Table 7: Inspection Summary

Site Number	Study Site	Location	Number of Patients	Classification
1100	Sainte Justine Hospital	Montreal, QC, Canada	4	NAI
1351	Hospital Sant Joan de Deu	Barcelona, Spain	5	NAI
1401	The Children's Hospital of Philadelphia	Philadelphia, Pennsylvania	10	VAI
1404	University of Michigan Comprehensive Cancer Center	Ann Arbor, Michigan	2	VAI
1406	University of Minnesota	Minneapolis, Minnesota	3	NAI

Table 7: Inspection Summary

Site Number	Study Site	Location	Number of Patients	Classification
1412	Doernbecher Children's Hospital	Portland, Oregon	2	VAI
NAI = No Action Indicated; VAI = Voluntary Action Indicated				

Reviewer Comments: I have reviewed the inspection summary for the BLA 125646 and concur with BIMO that the findings of the inspections did not impact the data submitted in the BLA or the analysis of efficacy or safety for tisagenlecleucel.

3.3 Financial Disclosures

Covered clinical study (name and/or number): CCTL019B2202, CCTL019B2205J, CCTL019B2101J, CCTL019B2102, CCTL019A2201		
Was a list of clinical investigators provided:	Yes X☐	No ☐ (Request list from applicant)
Total number of investigators identified: 386		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 4 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
Is an attachment provided with the reason:	Yes X☐	No ☐ (Request explanation from applicant)

Of the 6 investigators with certification of due diligence (Form3454), all provided disclosable financial interests/arrangements. Five of six investigators are at the University of Pennsylvania.

Thirteen patients were enrolled or screened for B2202 at the Children's Hospital of Pennsylvania (affiliated with the University of Pennsylvania). Nine had ORR (8 CR and 1 CRi). The sixth investigator with a report of a conflict is from the Children's Mercy Hospital in Kansas City, Missouri. This site enrolled 3 patients, all were responders. From the sites noted 16 patients total were screened, 12 were responders, 1 was treated and died before evaluation on day 28, and 3 were not treated due screening failure. If these patients are removed from the final analysis, the ORR is 80% based on ORR using CR/CRi assessment. After review of these documents, the potential financial or other conflicts of interest do not appear to impact the overall assessment of efficacy and safety for the BLA.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Tisagenlecleucel is comprised of genetically-modified antigen-specific autologous T cells that have been reprogrammed to include a chimeric antigen receptor (CAR) protein consisting of an extracellular portion that has a murine anti-CD19 single chain antibody fragment (scFv) and an intracellular portion that contains T-cell signaling (CD3-ζ) and co-stimulatory (4-1BB) domains. The target antigen is CD19 which is expressed on the surface of normal B cells and tumors derived from B cells. These signaling domains allow (CD3ζ and 4-1 BB) activation, persistence *in vivo,* and anti-tumor activity of the T cells. In addition, the product also contains Plasma-Lyte A injection (31.25% volume wide [V/V]), Dextrose in sodium chloride (NaCl) injection (same concentration, same unit), Dextran 40 in Dextrose injection (10%, same unit), Human Serum Albumin (HSA) (20%, same unit), and Cryoserv® dimethylsulfoxide (DMSO) (7.5%).

The applicant in version 4 of Study B2202 added a comparison of manufacturing site products to the safety and efficacy endpoints in the protocol. They have opened a new manufacturing plant at the Fraunhofer Institute in Germany (FI) to make tisagenlecleucel. Formal comparability between the product manufactured in the initial manufacturing site in Morris Plains, New Jersey (MP) and FI has not been done. Therefore efficacy analysis for the B2202 has been done on patients who received product from MP only.

There are theoretical risks associated with retroviral1 vector-based gene therapy products, including the potential for generation of replication-competent retroviruses (RCR) and vector-induced genotoxicity. Strategies to mitigate these risks, such as modification of the lentivirus for transduction, comprehensive RCR testing of the retroviral vector and tisagenlecleucel, and patient monitoring for delayed adverse events related to insertional mutagenesis occurred in the IND phase.

There are also risks to the excipient components of the tisagenlecleucel infusion. Allergic reactions and/or infusion reactions have been reported with serum albumin, and DMSO.

Reviewer Comment: Please see safety review section. There were no acute infusion reactions recorded for tisagenlecleucel. The risk of vector-induced genotoxicity will be monitored in the postmarketing study with assessments of second malignancy RCR testing is performed during the manufacturing process for tisagenlecleucel. There were no reports of a positive RCR result in the BLA.

4.2 Assay Validation

Per the FDA CMC reviewer, the assays that were utilized to determine immunogenicity were validated.

4.3 Nonclinical Pharmacology/Toxicology

The nonclinical studies evaluating tisagenlecleucel demonstrated the specificity of the CD19-binding domain of the transgene and the *in vitro* and *in vivo* proof of concept anti-tumor activity. A genomic insertion site analysis in 14 of samples was consistent with well-known patterns for lentiviral integration and no clonality was observed. *In vitro* expansion studies with tisagenlecleucel from healthy donors and patients showed no evidence for transformation and/or immortalization of T cells.

Tisagenlecleucel is a human-specific product, so classic toxicology studies would not be applicable. Classical genotoxicity assays and carcinogenicity assessment in rodent models were not performed for tisagenlecleucel. No preclinical reproductive studies have been conducted with tisagenlecleucel to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if tisagenlecleucel constitutes a risk to pregnant women or fetuses.

4.4 Clinical Pharmacology

The clinical pharmacology of tisagenlecleucel was evaluated separately in two consultations, Clinical Pharmacology and Pharmacometrics. These are summarized below and the considerations related to the clinical review of efficacy and safety will be discussed in additional detail in Sections 4.4.1, 4.4.2, 4.4.3, 6, 7, and 8.

4.4.1 Mechanism of Action

Tisagenlecleucel is a CD19-directed genetically-modified autologous immunotherapy. The patient's own T cells are programmed with a transgene that encodes a CAR to target CD19. The CAR includes a murine single chain antibody variable fragment (scFv) which recognizes CD19 which is fused to intracellular signaling domains from 4-1BB (CD137) and CD3ζ. The CD3ζ initiates T-cell activation and antitumor activity while the 4-1BB enhances expansion and persistence of tisagenlecleucel cells. When the CAR binds to CD19 positive cells, it transmits a signal to promote T-cell activation, expansion, target T-cell elimination, and persistence of tisagenlecleucel cells.

4.4.2 Human Pharmacodynamics (PD)

CBER/OBE and CDER/OCP conducted a Pharmacometrics analysis of tisagenlecleucel (BLA125646) to inform the clinical review. The working group identified major regulatory questions. To address these issues, they used logistic regression models and piloted the use of visual effect plots. In addition, they used predictive pharmacokinetic (PPK) models to explore the association between CAR-T kinetics and the clinical outcomes.
Summary analysis results and conclusions:

- A univariate/multivariate statistical analysis on the key product attributes (bodyweight adjusted/unadjusted cell dose, interferon-gamma (IFN- γ) level in the final product bag, vector batch, and transduction efficiency, did not reveal any significant correlation of these attributes with occurrence of Grade 3/4 CRS ($p>0.1$). The visual effect plots show weak correlation between the dose of transduced CAR T cells and the grade 3/4 CRS.

The consult found that IFN-γ level in the product was positively correlated with overall remission rate (ORR) at day 28 (p=0.08).

- No significant impacts of corticosteroid administration following tisagenlecleucel infusion were found through either a regression analysis on ORR at day 28 or a Kaplan-Meier model analysis on duration of response.
- A univariate analysis was conducted to evaluate patient-related demographic factors and baseline tumor burden (%blast cells, %MRD in blood, %MRD in bone marrow) on ORR at day 28. They identified a statistically significant correlation between percent blast cells count (% blast cells) and ORR.
- The analysis showed prior hematopoietic stem cell transplantation has no discernable association with ORR at day 28.
- Multiple classification models (Logistic Regression, Decision Trees, and Random Forest) and several variable selection methods were explored. The results indicated serum cytokines, ferritin, IFNG, IL10, IL12, IL13, IL2, IL4, IL6, IL8 and TNF, are significantly associated with occurrence of grade 3/4 CRS.
- Serum cytokines, C Reactive Protein, Ferritin and IL10, are significantly associated with ORR at day 28. Samples were collected at multiple time points post-tisagenlecleucel with a baseline at the time of screening (for example, Days 4, 7, 11, 14, 21 and 28 in the month post-tisagenlecleucel.
- The analysis indicates that a higher CAR-T expansion rate was associated with higher probability of CRS onset. A more rapid declining rate of CAR-T is associated with a higher likelihood of CRS remission in the next time interval. Besides CAR-T changing rate, a greater CAR-T concentration is associated with higher probability of CRS onset. These relationships between CRS status change and CAR-T kinetics were statistically significant.
- A trend that non-responders had slower CAR-T expansion and longer time to peak concentration was observed. The analysis did not show a statistically significant relationship between T-cell persistence (declining rates) and relapse.

In summary, due to small sample size, missing data and confounding factors associated with the clinical trial data, the exploratory analysis results should be interpreted with caution. Most of the results are inconclusive based on the currently available data. The analysis indicates CAR-T kinetics (such as expansion rate) is associated with both treatment response and occurrence of cytokine release syndrome (CRS). Therefore, it may be a potential predictor for both clinical safety and efficacy. In future work, more sophisticated PPK modeling of CAR-T and cytokines may be conducted to identify CAR-T kinetics profiles for a better treatment response and reduced risk of severe CRS.

Reviewer Comment: The Pharmacometrics consultation from CBER and CDER viewed these analyses as exploratory. Since this is the first-in-class for a CAR T cell application, the clinical team thought that we should have a review of the Pharmacometrics data for B2202 and see if there were potential signals to be followed up with subsequent applications for new indications for this product. There may be predictive value to certain cytokines (C Reactive Protein, Ferritin and IL10) on ORR at day 28. However, these are all markers for inflammation and with a 79% incidence of CRS after tisagenlecleucel infusion, it will be difficult to discern the value of these markers in the context of a study with a small sample size. Future applications for

tisagenlecleucel and pharmacometric studies will be needed to confirm findings. (See full consultative review for Pharmacometrics of tisagenlecleucel).

4.4.3 Human Pharmacokinetics (PK)

Per CBER Clinical Pharmacology Reviewer:

Following tisagenlecleucel infusion:

- There is an initial rapid expansion with a maximal concentration (Cmax) around Day 10, with a slower bi-exponential decline in CR/CRi (CR with incomplete hematological recovery) patients on Day 28. Cmax and area under the curve days 0-28 (AUC_{0-28d}) were higher in CR/CRi than non-responders (NR) but the numbers of NR are small.
- No difference noted for race, gender. Patients less than 10 years may have higher Cmax and AUC_{0-28d} but the numbers are small
- Dose response indicates that there is a plateau at weights greater than 50 kg. There is no relationship between dose and Cmax or $AUC_{0-28d.}$
- Treatment failures had lower Cmax and $AUC_{0-28d.}$
- Trend toward AUC_{0-28d} greater than the median had more durable remissions.
- Trend for patients with AUC_{0-28d} greater than the median to have slower B-cell recovery than in patients with higher AUC_{0-28d}.

Immunogenicity:

- Pre-infusion of tisagenlecleucel, 90% of the patients on B2202 had anti-mCAR19 antibodies. This did not affect expansion or cellular kinetics.
- There is no apparent relationship between pre-existing or treatment induced anti-mCAR19 antibodies on the cellular kinetics or impact on response or relapse.

Tumor Burden:

- Cmax and AUC_{0-28d} were higher with greater tumor burden.

Tocilizumab:

- CR/CRi patients (n=18) treated with tocilizumab had 265% and 183% higher CTL019 AUC_{0-28d} and Cmax, respectively as compared to patients (N=44) that did not receive tocilizumab as measured by qPCR
- CR/CRi patients that received corticosteroids had 89% higher AUC_{0-28d} compared with CR/CRi patients that did not receive corticosteroids

No impact on Cmax and AUC_{0-28d} was noted in patients based on disease status (relapse versus refractory) or prior HSCT.

Reviewer Comment: For additional information, please see the Clinical Pharmacology review. These studies again identify trends but due to small numbers, are not definitive. Early expansion at day 10 with slow decline correlates with responses of CR/CRi. Lower Cmax and AUC_{0-28d} was seen with non-responders. Again, we will need additional information with other applications for tisagenlecleucel to establish the validity of these early findings.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data. The results are incorporated into Sections 6, 7, and 8 of this review.

4.6 Pharmacovigilance

Risk Evaluation Mitigation Strategies (REMS)
The available safety data suggests that a Risk Evaluation and Mitigation Strategy (REMS) with an ETASU is indicated and the applicant was sent a notification letter on June 27, 2017. The recommended REMS to ensure that the benefits of tisagenlecleucel outweigh the risks of Cytokine Release Syndrome (CRS) and neurotoxicity includes:

Elements to Assure Safe Use (ETASU): The REMS should include ETASU to mitigate the known risks of CRS and neurotoxicity, as follows:

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified.
- Tisagenlecleucel is dispensed to patients only in certain health care settings.

Implementation System: The REMS should include an implementation system to monitor, evaluate, and work to improve the implementation of the ETASU that require health care settings that dispense the drug be specially certified and the drug be dispensed to patients only in certain health care settings, specifically, certified hospitals and affiliated clinics with appropriate access to tocilizumab. The applicant was asked to include an intervention plan to address any findings of non-compliance with the elements to assure safe use and to address any findings that suggest an increase in risk.

Existing procedures for the training and certification of the investigational sites (e.g., affiliated outpatient clinics and hospitals) will be included in the REMS with the modifications indicated below. The applicant was asked to incorporate the components of their REMS Communication Plan into the ETASU.

For hospitals:

1. To become certified to dispense tisagenlecleucel, hospitals and associated clinics must:

    a. Designate an authorized representative on behalf of the hospital.
    b. Ensure the authorized representative is assigned to the program for tisagenlecleucel and oversees implementation and compliance with the Tisagenlecleucel REMS Program requirements by the following:
        i. Complete the training and successfully complete the *Tisagenlecleucel REMS Program Knowledge Assessment.*
        ii. Ensure all relevant staff involved in the prescribing, dispensing or administering of tisagenlecleucel are trained on the REMS Program requirements per the training materials and successfully complete the *Tisagenlecleucel REMS Program Knowledge Assessment*, and maintain a record of training.
        iii. Goals of the training include: Informing prescribers and other staff about the risks, clinical manifestations, and management of cytokine release syndrome (CRS) and neurotoxicity with tisagenlecleucel.

c. Put processes and procedures in place to ensure the following requirements are completed prior to dispensing and administering tisagenlecleucel:
   i. Verify tocilizumab (two doses) is ordered and available for administration before a dose of tisagenlecleucel is administered.
   ii. Instruct families and patients that, they must remain within 2 hours of the hospital that administered the tisagenlecleucel for 3-4 weeks, so that if they develop CRS or neurotoxicity, they can return.
   iii. The patient and family: wallet cards to remind them of the signs and symptoms of CRS and neurotoxicity that require medical attention.

2. As a condition of certification:

a. The certified hospital must recertify if the hospital designates a new authorized representative or if additional healthcare personnel are added to their staff. Routine re-education of all staff by the certified hospital representative should be included in the REMS plan.
b. Report any adverse events suggestive of cytokine release syndrome, neurotoxicity, or suspected unexpected serious adverse reactions (SUSARS) to the tisagenlecleucel.
c. Maintain documentation for the Tisagenlecleucel REMS Program, and provide this documentation upon request to Novartis, FDA, or a third party acting on behalf of Novartis or FDA.
d. Comply with audits by the applicant, FDA, or a third party acting on behalf of the applicant or FDA to ensure that all processes and procedures are in place and are being followed for the Tisagenlecleucel REMS Program.
e. Dispense tisagenlecleucel to patients only after verifying tocilizumab is ordered and ready for administration within 2 hours of the order. A second dose must also be available.

For the applicant:

3. To implement the Tisagenlecleucel REMS Program in hospitals, Novartis must:

a. Ensure that hospitals that dispense tisagenlecleucel are certified, see above.
b. Provide initial live training for healthcare providers who prescribe, dispense, or administer tisagenlecleucel to ensure that the hospital can complete the certification process for the Tisagenlecleucel REMS Program for new dispensing institutions. For recertification for the Tisagenlecleucel REMS Program, the training should be placed on a website accessible to treatment sites for tisagenlecleucel.
c. Ensure that hospitals are notified when they have been certified by the Tisagenlecleucel REMS Program.
d. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the certified hospital.
e. Provide the REMS materials listed below to all healthcare providers at new sites who: (1) attempt to order tisagenlecleucel and are not yet certified or (2) inquire about how to become certified.
   - *Tisagenlecleucel REMS Program Knowledge Assessment*
   - *Slides for Live Training/Hospital Training material(s)*
   - *Tisagenlecleucel REMS Program Hospital Enrollment Form*
   - *Tisagenlecleucel REMS Program website*
   - *Tisagenlecleucel Patient Wallet Card*

4. To further implement the Tisagenlecleucel REMS Program. Novartis must:
   a. Ensure that tisagenlecleucel is only distributed to certified hospitals.
   b. Maintain a validated secure database of hospitals that are certified to dispense tisagenlecleucel in the tisagenlecleucel REMS Program.
   c. Maintain records of tisagenlecleucel distribution and dispensing to certified hospitals to meet the REMS requirements.
   d. Maintain a Tisagenlecleucel REMS Program Call Center and a REMS Program Website. The REMS Program Website must include the option to print the Package Insert, the Medication Guide, and tisagenlecleucel REMS materials. The tisagenlecleucel product website must include a prominent REMS-specific link to the tisagenlecleucel REMS Program Website (not the reverse).
   e. Ensure that Tisagenlecleucel REMS Program website is fully operational and the REMS materials listed in or appended to the tisagenlecleucel REMS document are available through the tisagenlecleucel REMS Program Website and by calling the tisagenlecleucel REMS Program Call Center.
   f. Monitor that the certified hospitals are evaluating their training program on a regular basis to ensure the requirements of the tisagenlecleucel REMS Program are being met; institute corrective action if noncompliant, and decertify hosptials that do not maintain compliance with the REMS.
   g. Maintain an ongoing annual audit plan that involves hospitals and audit all newly certified hospitals within 180 calendar days after the hospital places its first order for tisagenlecleucel to ensure that all processes and procedures are in place and functioning to support the requirements of the Tisagenlecleucel REMS Program.
   h. Take reasonable steps to improve implementation of and compliance with the requirements in the Tisagenlecleucel REMS Program.

The Pharmacovigilance Reviewer also concluded that long-term safety in patients treated with tisagenlecleucel needs to be confirmed as a postmarketing requirement (PMR). The applicant has submitted a postmarketing Study CCTL019B2401 (B2401) as the means to address the PMR.

Study B2401 is a multicenter, prospective, observational, non-interventional, planned safety study. The intent is to follow the recipients of tisagenlecleucel for 15 years to assess RCR, persistence, and the potential for insertional mutagenesis with tisagenlecleucel that is transduced with a lentivirus. The planned enrollment to be recommended by FDA is 1000 patients enrolled within 3 months of tisagenlecleucel infusion (enrollment period of 5 years). All enrolled patients will be followed for 15 years from their tisagenlecleucel infusion. Standard of care follow-up for pediatric and young adult ALL patients will be done. The FDA recommended endpoint will be evaluation for second malignancy which will include tissue work-up by the applicant for these events. Secondary endpoint will be adverse events and laboratory abnormalities, adverse events of special interest (CRS, neurotoxicity, infections, prolonged cytopenias), growth and development, reproductive status and pregnancy outcomes, and disease outcomes (ORR, OS).

Reviewer Comment: The REMS with ETASU and the PMR study are the recommendation of the clinical review team with concurrence from the pharmacovigilance reviewers from CBER OBE, CDER DRISK, and the CBER Safety Working Group (REMS on 6/8/2017; PMR on 7/13/2017). The goal of the REMS is to assure that sites are prepared for the safety risks of tisagenlecleucel which were identified in the IND phase of product development. The PMR

B2401 study addresses the theoretical concerns of insertional mutagenesis or the development of a tisagenlecleucel related second malignancy. With the occurrence of a second malignancy, the applicant will contact the site and ask for tissue to confirm that the second malignancy is not related to tisagenlecleucel. This is a heavily pretreated population of patients with an established risk of second malignancy. It is important to establish whether or not tisagenlecleucel has increased that risk.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

One single-arm trial supported the BLA application, CCTL019B2202 (B2202). Two secondary studies that utilized the UPenn CTL019 product were provided for safety and efficacy comparison (CCTL019B2205J [B2205J] and CCLT019B2101J [B2101J]). Two additional studies were included in the application. They were both conducted at UPenn. CCTL019B2101J (UPCC04409) which was a pilot study of anti-CD19 CAR T cells in CD19+ leukemia and lymphoma. Six patients with acute lymphoblastic leukemia (n=6) were treated. The mean age of the adult ALL patients was 50 years (SD 15.77) and one was under 40 years of age (26 years, diagnosed at age 18). CCTL019A2201 was a dose optimization trial for patients with CD19+ CLL. No formal comparability study of tisagenlecleucel and the University of Pennsylvania and Children's Hospital of Philadelphia (UPenn) CTL019 has been done, and there are differences in the (b) (4) and different manufacturing processes that precludes comparability without appropriate analysis. Therefore, this review will limited to B2202 for safety and efficacy.

The primary efficacy and safety analyses for the BLA were based on data from Study B2202. Eighty-eight patients were enrolled. Sixty-eight patients received tisagenlecleucel from the U.S. (n=63) or the German (n=5) manufacturing sites.

This clinical review for efficacy focused on the 63 patients treated with tisagenlecleucel from the U.S. manufacturing plant in Morris Plains, New Jersey and focused on the confirmation of the primary endpoint of best overall remission rate (ORR, equals complete remission [CR] plus CR with incomplete hematologic recovery]) within 3 months of the infusion of tisagenlecleucel as determined by an independent review committee (IRC), secondary endpoints of status of minimal residual disease at time of best overall response (BOR), duration of response, overall survival, and relapse-free survival. This was accomplished with a review of the submitted electronic case report forms (eCRFs) for the primary endpoint and correlation with secondary endpoints such as relapse-free survival RFS at 3, 6, 9, and 12 months, and overall survival (OS) in the treated population.

The review of the safety data for the B2202 was performed in the 68 patients in the Safety Analysis set. Safety data was reviewed over two phases: enrollment to infusion and after infusion in the patients who received tisagenlecleucel. The review focused on adverse events of special interest after tisagenlecleucel, such as cytokine release syndrome (CRS), neuropsychiatric toxicity, persistent cytopenias after day 28, infections, febrile neutropenia, renal, hemorrhagic episodes, acute infusion reactions, and tumor lysis syndrome.

Reviewer Comment: We will not include any of the study data in the review from the University of Pennsylvania (UPenn) studies since the product was not made by Novartis in the submitted

data except for 3 cases. Comparability between the Novartis and UPenn products has not been established.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- IND 13960 electronic and paper documents and FDA reviews
- IND 16130 eCTD documents, datasets, and FDA reviews
- BLA 125646 eCTD documents, datasets, and amendments 0- 44 which include the Applicant's responses to IRs.

5.3 Table of Studies/Clinical Trials

Table 8: Clinical Studies to be used in the Analysis

Study Identifier	Study Design	Dosage Regimen: Route of Administration	Number of Patients	Patient Population	Primary Endpoint
B2202	**Single-arm, open-label, multi-center, Phase 2 study**	**Lymphodepleting chemotherapy followed 2-14 days later by a single intravenous infusion of tisagenlecleucel** **Dose: 0.2 to 5 $\times 10^6$ CTL019 cells (transduced viable T cells) per kg body weight (for patients ≤ 50 kg) and or 0.1 to 2.5$\times 10^8$ CTL019 cells (for patients >50 kg)**	**Target accrual = up to 95 patients enrolled** **N=107 signed consent and screened** **Enrolled N= 88** **Safety N= 68** **Efficacy N= 63**	• **Age ≥3 yrs. at screening and ≤21 yrs. at diagnosis** • **CD19+ B-cell ALL** – **≥2nd relapse** – **Relapse after HSCT** – **Refractory to at least 2 primary induction regimens**	**Best overall remission rate (ORR) (CR+CRi) within 3 months after infusion of tisagenlecleucel**

5.4 Consultations

Clinical Outcome Assessment (CDER):

The Clinical Outcome Assessment (COA) review provided consultation to the Center for Biologics Evaluation and Research (CBER) regarding BLA 125646 for the trial B2202. COA reviewed the Applicant's patient-reported outcome (PRO) instruments for this phase 3 clinical trial to assess health related quality of life (HRQoL).

PRO Instrument	Concept(s)	Endpoint[1]
PedsQL (children; 8-12 years)	Physical, emotional, social, and school functioning	Exploratory
PedsQL (teens; 13-17 years)		
PedsQL (adult; 18-25 years)		
EQ-5D-Y (children: 8-12 years)	Mobility; self-care; usual activity; pain/discomfort; anxiety/depression	
EQ-5D-3L (13 years and above)		

CBER consulted the COA Staff to assess the validity and reliability of the PedsQL, EQ-5D-Y, and EQ-5D-3L instruments to support medical product labeling claims.

The COA review concluded that the evidence submitted by the applicant is insufficient to demonstrate that the PedsQL, EQ-5D-Y, and EQ-5D-3L instruments are adequate to measure health-related quality of life (HRQoL) in the context of this drug development program. The PRO instruments do not appear to be well defined and reliable based on the COA review. This information should not be included in the label.

CBER OBE/CDER DRISK: see Section 4.6 for Pharmacovigilance, Post-Marketing Requirements and REMS ETASU.

CBER/CDER Pharmacometrics: See Section 4.4.2

CBER Clinical Pharmacology: See Section 4.4.3

5.4.1 Advisory Committee Meeting (if applicable)

An ODAC meeting was held on July 12, 2017 to discuss the safety and efficacy of Biologics License Application (BLA) 125646, tisagenlecleucel for the treatment patients age 3-25 years of age with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). The committee discussed the safety profile of tisagenlecleucel, risk mitigation for the licensed product, pharmacovigilance. The voting question queried whether there is a favorable benefit-risk profile with the appropriate risk mitigation for the treatment of R/R B-cell precursor ALL with tisagenlecleucel.

PROPOSED INDICATION: Treatment of pediatric and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)

Product Quality Discussion

Discussion Question #1: During tisagenlecleucel development, the applicant established product quality specifications to assess Chimeric Antigen Receptor (CAR) expression and T-cell activity, including transduction efficiency by flow cytometry, vector copy number per cell, and IFN-γ production following stimulation by CD19+ antigen presenting cells.

Please discuss the following aspects of the control of product quality of tisagenlecleucel with respect to identity, safety, purity and potency:

a. The design of the CAR construct and viral vector.

b. The assessment of CAR expression and T-cell activity through
   i. The number of transduced T cells
   ii. The number of vector copies per cell
   iii. Antigen-specific T-cell function (e.g., IFN-γ production and cytotoxicity upon stimulation)

c. Any other measurements, such as T-cell subpopulations (cell surface marker characterization), that could provide greater assurance of product quality.

Discussion Question #2: Potential safety concerns with tisagenlecleucel and other retrovirus-based gene therapy products include generation of replication-competent retrovirus (RCR) and insertional mutagenesis. Strategies to address these concerns include vector design and product testing.

a. Please discuss how vector design impacts the risk of RCR.

b. Please discuss how vector design impacts the risk that insertional mutagenesis might cause secondary malignancies.

c. Please discuss the extent to which product testing can mitigate the risk of RCR and insertional mutagenesis.

Clinical Discussion

Discussion Question #3: Please discuss risk mitigation measures for the serious risks of cytokine release syndrome and neurotoxicity with tisagenlecleucel.

Discussion Question #4: For the tisagenlecleucel IND studies, the FDA requires 15 years of follow-up to monitor for subsequent malignant transformation.

Given the possibility of generation of replication-competent retrovirus and insertional mutagenesis, please discuss the duration of follow-up and the type of assessments that you would recommend for patients who receive marketed tisagenlecleucel.

Voting Question #5: Considering the efficacy and safety results of Study B2202, is the benefit-risk profile of tisagenlecleucel favorable for treatment of pediatric and young adult patients (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia (ALL)?

Results of Discussion:
CMC #1: discussion of strategies to address safety concerns of retrovirus based therapy for possible RCR and insertional mutagenesis. The discussion centered on the design of the retroviral vector and the targeted cell (T cell versus stem cell; T-cell subpopulations), the types of cells in the final product, the potency of the product, and the construct of the lentiviral vector (a retrovirus) (possible insertion sites).

CMC #2: Discussion of the safety risk of RCR which committee member thought might no longer a safety risk. Insertional mutagenesis is considered a potential risk.

Clinical #3: Discussion of short-term safety risk mitigation on the B2202 trial and those anticipated for the commercial setting. This was to address CRS and other toxicities noted after the tisagenlecleucel infusion.

Clinical #4: Discussion of the planned 15 year follow-up centered on the B2401 postmarketing observational trial. Further discussion of RCR, insertional mutagenesis did not occur.

Voting Question #5: Considering the efficacy and safety results of Study B2202, is the benefit-risk profile of tisagenlecleucel favorable for treatment of pediatric and young adult patients (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia (ALL)?
Vote: Yes = 10 No = 0 Abstain = 0

5.4.2 External Consults/Collaborations

See Section 5.3

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (CCTL019B2202)

CCTL019B2202 (B2202): A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Pediatric Patients with Relapsed and Refractory B-Cell Acute Lymphoblastic Leukemia

6.1.1 Objectives

The primary objective of B2202 was to evaluate the efficacy of CTL019 therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment.

The key secondary objectives were to:

- Evaluate the efficacy of CTL019 therapy from U.S. manufacturing facility as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment
- Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from all manufacturing facilities
- Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from U.S. manufacturing facility

Other secondary objectives included to:

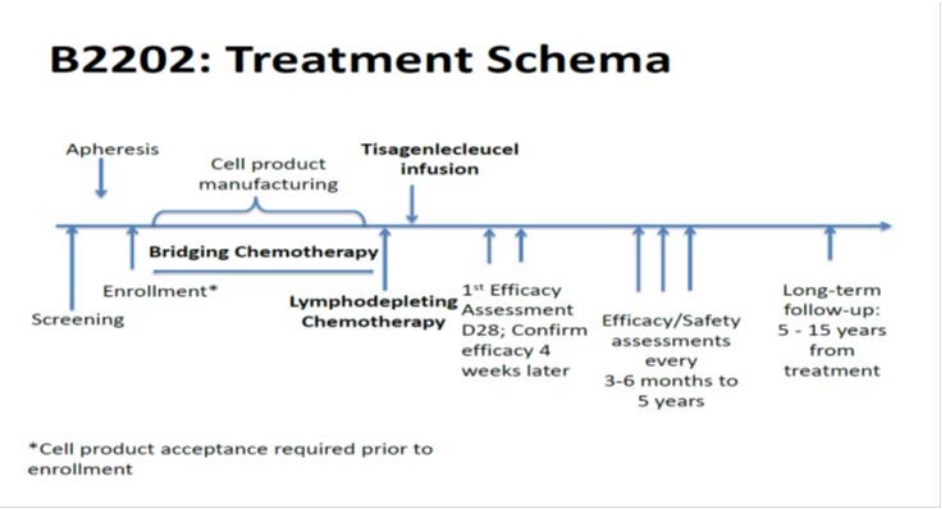
- Evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment
- Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment
- Evaluate the duration of remission (DOR)
- Evaluate the relapse-free survival (RFS)
- Evaluate the event-free survival (EFS)
- Evaluate the overall survival (OS)
- Evaluate the response at Day 28 +/- 4 days
- Evaluate the impact of baseline tumor burden on response
- Evaluate the quality of response using MRD disease assessments before treatment and at day 28 +/- 4 days after treatment using central assessment by flow cytometry and before SCT by local assessment (flow or PCR)
- Evaluate the safety of CTL019 therapy
- Characterize the in vivo cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, CSF, and other tissues if available)
- Describe the prevalence and incidence of immunogenicity to CTL019
- Describe the effect of CTL019 therapy on Patient Reported Outcomes (PRO)
- Derivation of a score to predict cytokine release syndrome
- Describe the profile of soluble immune factors that may be key to cytokine release syndrome
- Describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion for safety monitoring
- Assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by Fraunhofer Institute

6.1.2 Design Overview

B2202 is a Phase 2, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia.

The patient events were conducted in sequential phases:

- Screening: Informed Consent, apheresis
- Pre-Treatment (manufacturing, bridging chemotherapy, and lymphodepletion)
- Treatment and primary follow-up to 12 months
- Secondary follow-up to 5 years
- Long-term follow-up (survival and second malignancy) to 15 years on separate study (CCTL019A2205B).



Source: Derived from B2202, BLA Section 5.3.5.2 Study report B2202, Appendix 16

Reviewer Comment: The primary endpoint of Study B2202 was overall remission rate (complete response [CR] + CR with incomplete hematologic recovery [CRi]) with confirmation as determined by an IRC. This design allows for initial efficacy assessment at day 28 with follow-up monthly until 6 months.

6.1.3 Population

Key inclusion criteria are:

- Relapsed or refractory pediatric (3 -21 years at screening up to 21 at time of original diagnosis) B-cell precursor ALL.
    - Relapse was defined as
        - Presence of > 5% blasts at screening
        - Second or subsequent bone marrow (BM) relapse, or
        - Any BM relapse after allogeneic SCT and must be ≥ 6 months from SCT at the time of tisagenlecleucel infusion
    - Refractory was defined by not achieving an initial CR after 2 cycles of a standard chemotherapy regimen (primary refractory). Patients who were refractory to subsequent chemotherapy regimens after an initial remission were considered chemorefractory
- Patients with Ph+ ALL were eligible if they are intolerant to or have not achieved a remission after two lines of TKI (tyrosine kinase inhibitor) therapy, or if TKI therapy is contraindicated, or ineligible for allogeneic SCT because of:
    - Comorbid disease
    - Other contraindications to allogeneic SCT conditioning regimen
    - Lack of suitable donor
    - Prior hematopoietic stem cell transplant (HSCT)
    - Declined allogeneic HSCT as a therapeutic option
- CD19 tumor expression in bone marrow (BM) or peripheral blood (PB) within 3 months of study entry
- Adequate organ function
- Karnofsky/Lansky score ≥ 50
- Apheresis product received and accepted by manufacturing site

Key Exclusion criteria:

- Isolated extra-medullary relapse
- Concomitant genetic syndrome, with the exception of Down Syndrome
- Burkitt's lymphoma/leukemia
- Treatment with any prior gene therapy product, anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
- Active hepatitis B, C, or any uncontrolled infection
- Grade 2 to 4 Graft versus Host Disease (GVHD)
- Medications or treatments that were to be excluded:
    - Corticosteroids within 72 hours of tisagenlecleucel infusion, with the exception of physiologic replacement
    - Allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion
    - GVHD therapies
    - Chemotherapy stopped prior to lymphodepletion based on clearance
    - CNS prophylaxis treatment
- Active central nervous system (CNS) disease (CNS 2 disease [CSF containing blasts, but < 5 WBCs/microliter] patients were eligible)

Reviewer Comment: As outlined by the eligibility criteria, the population was intended to be highly resistant to conventional therapy. CD19 positivity was confirmed within 3 months of study entry. This was in response to reports of CD19 negative relapse after treatment with the University of Pennsylvania CTL019 and to insure that treatment failures were not due to the treatment of ALL that was not positive for CD19.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Apheresis:
Per local institutional guidelines or the applicant's protocol (CCTL019B2206)

Manufacturing Period:
Apheresis product is shipped to Morris Plains, New Jersey for processing. Once accepted, patient is enrolled.

Bridging chemotherapy:
Investigator choice after apheresis product accepted at manufacturing site.

Lymphodepletion (LD): mandated per protocol if white blood count (wbc) was greater than 1 x 10^9/L.

- Fludarabine (30 mg/m^2 intravenously [i.v.] daily for 4 doses) and cyclophosphamide (500 mg/m^2 i.v. daily for 2 doses starting with the first dose of fludarabine)

- Alternative regimen if unable to tolerate cyclophosphamide: Cytarabine (500 mg/m^2 i.v. daily for 2 days) and etoposide (150 mg/m^2 i.v. daily x 3 days starting with the first dose of cytarabine)

6.1.5 Directions for Use

Eligibility criteria for the tisagenlecleucel infusion (key):

- Negative influenza testing
- No significant change in Karnofsky/Lansky score from screening
- No significant deterioration in organ function since screening
- Leukemia status: No accelerating disease as evidenced by increasing WBC count, increased organomegaly, evidence of new CNS disease
- Chemotherapy toxicity > Grade 1 or greater than baseline for the following adverse events warranted delay of the tisagenlecleucel infusion
    - Requirement for supplemental oxygen
    - New cardiac arrhythmia
    - Hypotension with pressor support
    - Infection: uncontrolled, including bacterial, fungal, and viral infections within 72 hours of planned tisagenlecleucel infusion.
        - Documented improvement in infection must be obtained before infusion of tisagenlecleucel.
    - Grade 2-4 GVHD
    - Patient requiring concomitant medications listed in exclusion criteria at screening
    - Recent HSCT
    - If > 4 weeks from LD, may require repeat LD chemotherapy if white blood count (WBC) > 1 x 10^9/L.
    - Change in cardiac status from screening
    - Positive pregnancy test

Reviewer Comment: These criteria were established to prevent infusion in a clinical setting that the IND phase of development had identified as safety concerns with the infusion of a CAR T cell. In general, they define a patient with a moderately deteriorating clinical status with rapidly progressing ALL, and/or persistent toxicities from recent chemotherapy, and/or a newly acquired active infection, who would be harmed by the therapy. These stipulations will be included in the label.

Tisagenlecleucel infusion:

- Give 2-14 days after completion of LD
- Confirmation that a dose of tocilizumab is available on site prior to tisagenlecleucel infusion
- Premedication with acetaminophen or paracetamol and diphenhydramine or an H1 antihistamine.
- Cell thawing and infusion
- Physician must document patient met infusion criteria
- Dose was weight-based:
    - For patients ≤ 50 kg: single intravenous (IV) dose of 0.2 to 5 x 10^6 viable transduced T cells /kg body weight
    - For patients > 50 kg: single IV dose of 0.1 to 2.5 x 10^8 viable transduced T cells

Reviewer Comment:
The infusion of tisagenlecleucel requires expertise in cell processing and administration. The product was shipped frozen to the treatment centers and not thawed until a physician asserted that the patient was eligible to receive the product. These instructions will be included in the label for tisagenlecleucel.

6.1.6 Sites and Centers

Patients were enrolled and treated in 25 centers across U.S., EU, Canada, Australia, and Japan. In the U.S., 13 centers enrolled 50 patients. Canada had 2 centers and enrolled 6 patients. Europe had 8 centers and enrolled 28 patients. Japan had one center and enrolled 3 patients. Australia had one center and enrolled one patient.

6.1.7 Surveillance/Monitoring

The evaluations and monitoring mandated by B2202 are included in the Table 33 Appendix B.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint

- Overall remission rate (ORR) assessment during the 3 months after tisagenlecleucel administration; ORR includes CR and CRi, as determined by independent review committee (IRC) assessment from all manufacturing sites.

Key Secondary efficacy endpoint

- ORR assessment which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment at U.S. sites
- Percentage of patients who achieve a best overall response (BOR) of CR or CRi with an MRD-negative bone marrow by central analysis using flow cytometry, among all patients who receive tisagenlecleucel
- Percentage of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry (< 0.01%) during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from U.S. manufacturing facility. See below for information on MRD testing laboratory.

Secondary Endpoints

- Percentage of patients who achieve best overall response (BOR) of CR or CRi at Month 6 without stem cell transplant (SCT) between tisagenlecleucel infusion and Month 6 response assessment.
    - To evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment
    - Description of all patients who proceed to SCT
- Duration of remission (DOR) or the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL; summarize site of relapse
- Relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS).
- Response at Day 28 +/- 4 days
- Response based on baseline tumor burden
- MRD quantitative result and qualitative result
- Type, frequency, and severity of adverse events and laboratory abnormalities.
    - CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available
    - Expression of CTL019 detected by flow cytometry in blood and bone marrow
    - Cmax, Tmax, AUCs and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF if available
    - Persistence of CTL019 in blood, bone marrow, and CSF if available (e.g. Mean Residence Time [MRT] last)
    - Prevalence and incidence of immunogenicity and anti-CTL019 assay titers
    - PRO as measured by PedsQL and EQ-5D questionnaires

- Develop a score utilizing clinical and biomarker data and assess its ability for early prediction of cytokine release syndrome
- Frequent monitoring of concentrations of soluble immune factors in blood
- Lymphocyte subsets of B and T cells and description of associated safety events
- ORR and MRD negative remission
- Type, frequency and severity of adverse events and laboratory abnormalities
- CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available

The pre-specified primary efficacy endpoint was an ORR of greater than 20% during the 3 months after tisagenlecleucel administration as measured by the Independent Review Committee, per modified NCCN Guidelines for response in ALL as detailed in Table 9 .The ORR is defined as the proportion of patients with a best overall disease response of CR or CRi, where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until the start of new anticancer therapy.

Best response was to be assigned according to the following order:

- CR
- CRi
- No response (NR): no evidence of a response.
- Unknown: patients who did not have an evaluation for CR or CRi in compliance with the guidelines.

Table 9: Definition of CR, CRi, and Relapse

Response Category	Definition
Complete remission (CR)	All of the following criteria are met:
	Bone Marrow • < 5% blasts
	Peripheral Blood • Neutrophils > 1 x 10^9/L, and • Platelets > 100 x 10^9/L, and • Circulating blasts < 1%
	Extramedullary disease • No evidence of extramedullary disease (by physical exam, *spinal tap (D 28 or to ascertain CR/CRi)*, and symptom assessment
	Transfusion independency • No platelet and/or neutrophil transfusion ≤ 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above are met, with the exception that the following exist: • Neutrophils ≤ 1 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L and/or • Platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Relapsed Disease	Only in patients who obtained a CR or CRi: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in the bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi

Source: Section 10.4.1 in the protocol B2202

Full response evaluation including blood, BM, LP, and physical exam was required to document initial CR or CRi determination (Day 28). If not in CR/CRi on D28, then the BM, LP, and physical exam was repeated in one month. If a CR or CRi was established, then confirmation was required as described below.

In order for the best ORR to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi.

MRD Measurement
MRD was measured by 8-color flow cytometry in an applicant affiliated lab (b) (4) . The stated lower limit of quantitation was 0.01% (See Module 5.3.5.2; dmpk-rb2202-mrd: Methodology for Quantitation of Minimal Residual Disease in Bone Marrow and Peripheral Blood in Study CCTL019B2202).

Reviewer Comment: FDA asked for the spinal tap as part of the assessment for ORR as part of the SPA concurrence. Patients with CNS2 disease were permitted on the trial. This is to not only confirm no new disease but to also confirm the status of the pre-existing CNS disease which is not possible with a physical exam and a symptomatic approach. Tisagenlecleucel has been proposed as able to cross the blood/brain barrier and this granular assessment of CNS disease is necessary to assure the accuracy of the results.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size
The protocol stated that an ORR of 45% that excludes a 20% ORR would indicate meaningful efficacy in this highly refractory population. Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR >20%, it was estimated that 76 patients in the FAS would provide more than 95% power to demonstrate statistical significance at one-sided cumulative 0.025 level of significance, if the underlying ORR is 45% and taking into account the interim analysis. To allow for dropouts, up to 95 patients were to be enrolled.

Timing of Analyses
Per protocol, an interim analysis was to be performed when the first 50 patients who received tisagenlecleucel had completed 3 months of follow-up from day of infusion or discontinued earlier. The final analysis of the primary endpoint was to be performed after all patients infused with tisagenlecleucel have completed 3 months follow-up from day of infusion or discontinued earlier. In addition, selected efficacy and safety analysis will be updated annually. A final Clinical Study Report (CSR) will be produced once all patients have completed the study.

Analysis Populations
- The enrolled set includes all enrolled patients whose leukapheresis product is received and accepted for manufacture.
- The full analysis set (FAS) includes patients who received tisagenlecleucel. The final efficacy analysis was to be performed on patients in the FAS. The interim analysis set included the first 50 patients of this population.

- The safety analysis set includes all patients who received at least one infusion of tisagenlecleucel.

Methods

Calculation of the primary endpoint: The ORR was to be calculated as a proportion with the 2-sided 95% exact Clopper-Pearson confidence intervals. Patients in the study who are of unknown clinical response will be treated as non-responders. If there is evidence of relapse, the overall response will be assessed as "relapsed disease" with the relapsed component alone.

Multiplicity: The primary efficacy endpoint was to be analyzed at the interim analysis and final analysis in a group sequential design. The study protocol proposed to control the type I error probability using a Lan-DeMets (O'Brien-Fleming) alpha-spending function at a one-sided 2.5% level of significance.

The hypothesis testing of the key secondary endpoint would be performed only when the hypothesis of the primary endpoint is rejected, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. In testing the key secondary endpoint, the type I error probability will also be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

If the interim analysis is performed with 50 patients, the final analysis includes up to 66 patients, and the lower bound of the 2-sided 98.0% exact CI of the ORR would need to be greater than 20% to declare statistical significance, an ORR of 18/50 = 36% is needed to claim success at interim. If the interim efficacy boundary is not crossed, a 2-sided 95.6% exact CI will be used at final analysis correspondingly. As a result, an ORR of 21/66 = 32% will be needed to claim success at final analysis (Study CTL019B2202 Section 10.7.2.1).

Statistical Methods for Secondary Endpoints:

- The proposed key secondary endpoint (MRD negative CR or CRi) will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with a coverage level according to the above alpha spending function.

- Duration of remission (DOR) is defined as the duration from the date when the response criteria of CR or CRi is first met to the date of relapse or death due to underlying cancer. DOR will be assessed only in patients with the best overall response of CR or CRi ("responders"). In case a patient does not have relapse or death due to ALL prior to data cutoff, DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be:

    - Ongoing without event
    - Lost to follow-up
    - Withdrew consent
    - New anticancer therapy (including HSCT)
    - Event after at least two missing scheduled disease assessments

In either case, the primary analysis will censor patients who undergo HSCT while in response to CTL019 at date of the transplantation. The applicant plans an exploratory analysis, the date of relapse or death (if due to the underlying cancer) after SCT will be used for DOR calculation.

- For overall survival (OS), in case a patient is alive at the date of last contact on or before data cutoff, OS is censored at the date of last contact. No censoring will be done in case of SCT. The distribution function of OS will be estimated using the Kaplan Meier method. The median OS along with 95% confidence intervals will be presented.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 10: Study B2202 – Patients Enrolled and Analyzed

	Total	Product from MP	Product from FH
Enrolled	88 patients		
Discontinued prior to tisagenlecleucel infusion	16 patients	15 patients	1 patient
Tisagenlecleucel infusion pending	4 patients	0 patients	4 patients
Tisagenlecleucel infused	68 patients	63 patients	5 patients

MP: Morris Plains, New Jersey manufacturing site; FH: Fraunhofer Institute, Germany manufacturing site

First patient enrolled: April 8, 2015
Data cut-off for efficacy analysis: November 23, 2016

The applicant revised B2202 to enable a comparability study for products manufactured in Morris Plains, New Jersey and at the Fraunhofer Institute in Germany. For the purposes of this review, the Safety Set of 68 patients included patients treated with products from both sites. The efficacy analysis is limited to the 63 patients treated with product from Morris Plains, New Jersey.

6.1.10.1.1 Demographics

Table 11: Demographics

Category	Subcategory	Enrolled Set* N=88 (%)	Safety Analysis Set N=68 (%)^	Efficacy Analysis Set N=63 (%)#
Performance Status at Baseline	Mean (SD) Median (min, max)	87 (13.5) 90 (50, 100)	87 (13.5) 90 (50, 100)	87 (13.5) 90 (50,100)
Response status at study entry	Chemo-refractory Primary refractory Relapse disease	9 (10%) 8 (9%) 71 (81%)	8 (12) 6 (9) 54 (79)	8 (13) 6 (9) 49 (78)
Number of Previous CRs	N Mean (SD) Median (Min-Max)	88 2.3 (1.4) 2 (0-6)	68 2.3 (1.47) 3 (1-8)	63 2.3 (1.47) 3 (0-6)

Table 11: Demographics

Category	Subcategory	Enrolled Set* N=88 (%)	Safety Analysis Set N=68 (%)^	Efficacy Analysis Set N=63 (%)#
Time from Diagnosis to first relapse N (%)	N < 18 months 18-36 months >36 months N/A	81 17 (21.0) 32 (39.5) 32 (39.5)	63 14 (22) 21 (34) 28 (44)	63 12 (19) 26 (41) 20 (32) 5 (8)
Time from most recent relapse to tisagenlecleucel infusion - months	N Mean (SD) Median (Min-Max)	Not defined for patients enrolled but not infused	62 4.1 (2.73) 3.4 (1.5-13.8)	63 3.2 (<1.5 – 13.8)
Number of Prior HSCT performed	0 1 2	36 (41%) 45 (51%) 7 (8%)	28 (41%) 35 (51%) 5 (8%)	28 (44) 30 (48) 5 (8)
Number of Previous Lines of Therapies	N Mean (SD) Median (Min-Max)	88 3.3 (1.65) 3 (1-8)	68 3.2 (1.47) 3 (1-8)	63 3.2 3 (1-8)

*Data not available for all patients in enrolled set. ^ patients treated with tisagenlecleucel made in U.S.
(Source: FDA statistical review, clinical review, and BLA, ADSL specific category and subcategory, for all three analysis sets: Enrollment, Safety and Efficacy; JReview)

Reviewer Comment: The study population (see Table 11*) is reasonably representative of the general population of pediatric and young adult patients with R/R ALL in the U.S.. For tisagenlecleucel, 48% had one prior HSCT, 8% had two prior HSCT, and the average number of prior chemotherapy regimens was 3.2. Seventy-eight percent of the patients were relapsed and 8% were primary refractory. All patients were required to have greater than 5% blasts in their screening bone marrow so were by definition in relapse. So with a median number previous CRs of 3, at least half of the patients were in their 3rd or 4th relapse. All were either primary refractory or in second or greater relapse. This is a highly refractory/resistant population of pediatric and young adult patients with ALL. This will be reflected in the indication statement in the label with the definition of the population for tisagenlecleucel.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Not applicable.

6.1.10.1.3 Subject Disposition

Results of Manufacturing:
As of the November 23, 2016 data cut-off there were 8 patients recorded as manufacturing failures on B2202. Of the 8, 7 were attempted manufacture in MP and 1 at the Fraunhofer Institute (FI) in Germany. One patient died while a second attempt was made to manufacture tisagenlecleucel and is recorded as a death for the enrollment to infusion interval. None of the other 7 from MP and FI had additional manufacturing attempts.

Bridging chemotherapy:
Whether or not to give bridging chemotherapy after apheresis was investigator choice once the product was accepted at manufacturing site. Fifty-eight of the 68 (85%) patients, who received

tisagenlecleucel in the safety population, also received bridging chemotherapy prior to lymphodepletion. In the efficacy population, 55 (87%) received bridging chemotherapy.

Reviewer Comment: For the safety subset this reflects a 9% manufacturing failure rate. This proposed patient population is highly refractory and has a history of multiple regimens of chemotherapy and in some cases HSCT. This makes them more susceptible to infection, as well as from uncontrolled progression of their disease. This makes a second attempt at apheresis less feasible. The product is made from autologous T cells and there are mandated minimums for white blood count and T cells prior to apheresis. These failure rates delineate that in heavily pretreated patients in poor medical condition the absolute numbers of the WBC and T cells may not always reflect the suitability of the product baseline material. How this is considered in the assessment of efficacy is discussed in Section 6.1.11.1.

Lymphodepletion Therapy

Sixty-one of the 63 (98%) patients in the efficacy set received lymphodepleting chemotherapy prior to infusion of tisagenlecleucel (No LD (b) (6)). Sixty-five of the 68 (96%) patients in the safety set received lymphodepleting chemotherapy. Sixty-four received fludarabine plus cyclophosphamide [n=64], and 1 patient received cytarabine with etoposide. Twenty-three patients had WBC less than 1x 10^9/L at the start of their lymphodepletion phase. Three of these 23 patients did not receive lymphodepleting chemotherapy.

Reviewer Comment: Lymphodepletion therapy is designed to improve the efficacy of activated T cells by decreasing the immune cells in the patient. Patients with a WBC less than 1 x 10^9/L were not required to receive lymphodepleting chemotherapy (LD), but 98% did. There is insufficient information to conclude that the efficacy reported for this trial is independent of the lymphodepleting chemotherapy. This prescribed regimen with fludarabine and cyclophosphamide should be included in the tisagenlecleucel label, and it should in clear in the indication statement that tisagenlecleucel is for use with lymphodepleting chemotherapy.

Dose of tisagenlecleucel

For protocol specified dose and regimen, please refer to Treatment and Study Drug Administration Schedule above.

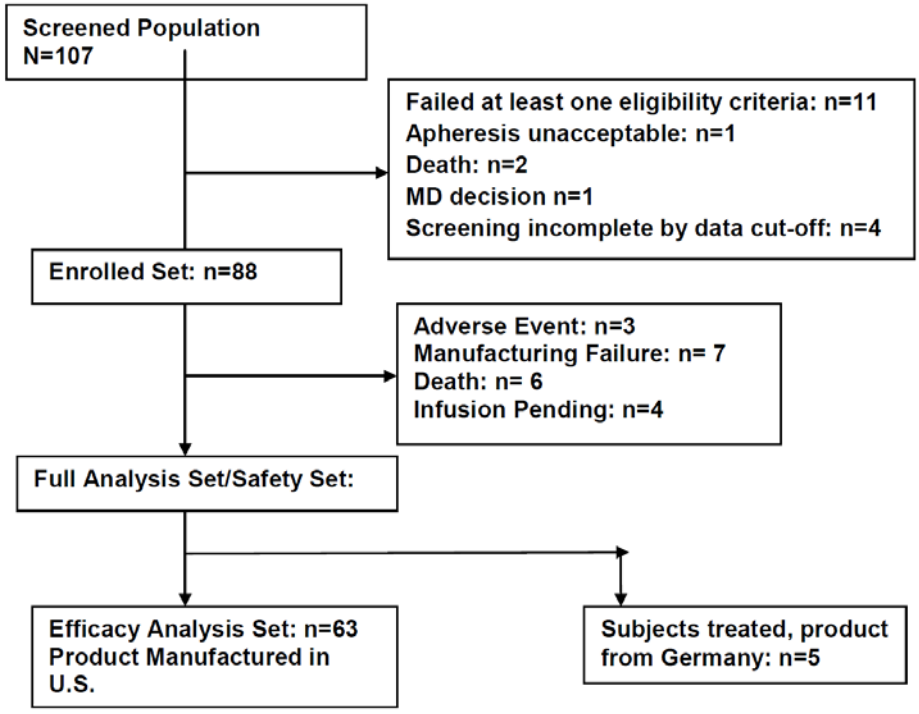
Table 12: Dose Administered for the Efficacy Set

Dose: Efficacy Set N=63 N (%)	
Below Target range	**5 (8%)**
Within Target Range	**56 (89%)**
Above Target Range	**2 (3%)**
Transduced viable T-cell dose (10e8 cells)	
Mean	**1.1**
Median	**1**
Min, Max	**0.03 – 2.6**
Weight Adjusted transduced viable T-cell dose infused (10e6/kg)	
Mean	**2.6**
Median	**3**
Min - Max	**0.19 – 5.4**

Source: ADEX

Reviewer Comment: The dose chosen for the study was based on the B2101J Study (Phase 1). Ninety percent of the patients received a dose within the range prescribed by the study B2202 guidelines. The dose used in the Study B2202 will be the dose recommended in the label. Product is made at Novartis manufacturing plants and based on the yield, the appropriate dose for the patient is placed in 1 -2 bags and shipped to the site with the bags clearly identified to be patient specific. This is also described in the label.

Figure 1: Patient Disposition from Screening to Efficacy Analysis Set



Source: FDA reviewer

Reviewer Comment: The purpose of this diagram is to highlight that not all candidates for tisagenlecleucel received the infusion. Even those who were deemed eligible had up to a 9% chance of a manufacturing failure, six died awaiting their infusion and 3 experienced an adverse event that precluded receiving tisagenlecleucel. This information will need to be clearly stated in the label.

Post-Study Treatment
Seven patients received HSCT in remission (6 CR or CRi, one Unknown) after receiving tisagenlecleucel. Fourteen patients went on to receive other chemotherapy without HSCT.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The pre-specified primary efficacy endpoint was overall remission rate (ORR), and there was one planned interim analysis. Based on the data available at the time of the interim analysis, the

study was considered a success, because the lower bound of the 2-sided 95% exact confidence interval for ORR was greater than 20%, so that the null hypothesis that the ORR was less or equal to 20% was rejected.

As indicated in Section 6.1.1, the primary objective was to be assessed in patients treated with product from all manufacturing sites. Since comparability was not yet established for the products from the FI site, the primary endpoint was assessed only for patients treated with product from the MP site. Although this is analysis is pre-specified as a key secondary objective, this approach is considered acceptable in this situation where the patients treated with FI product are not considered as treated and therefore would not be included in the Efficacy Population.

In the current analysis, a total of 52 patients (82.5%) in the Efficacy Set (n=63) had a best overall disease response of CR or CRi during the 3 months after tisagenlecleucel administration, as determined by Independent Review Committee (IRC). The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is 70.9%, which is above the pre-set null hypothesis rate. Of note, the magnitude of the ORR was driven by the CR component rather than the CRi's (Table 13). Among the 52 responders, forty patients (63%) had the best response of CR within the first 3 months after infusion, and 12 patients (19%) had the best response of CRi (Table 13). Among the 52 responders, the median duration of response (DOR) was not yet reached with the median follow-up of 4.8 months. All responses as recorded in the eCRF documents (local assessment and IRC) were confirmed by the FDA clinical reviewer.

Table 13: Efficacy Analysis Results

	Efficacy Analysis Set: Primary Endpoint* (n=63) n (%)	**Modified Enrolled Set (n=78) n (%)**
ORR (95% CI)	52 [82.5% (95% CI 70.9, 91.0)]	52 [66.7% (95% CI 55.1, 76.9)]
CR	40 [63.4% (95% CI 50.4, 75.3)]	40 [51.2% (95% CI 39.7, 62.8)]
CRi	12 (19%)	12 (15%)
NR/UNK	11 (17.5%)	11 (14%)

Source: FDA clinical and statistical reviewers;. Dataset ADEFIRC1
*All CR and CRi were MRD negative, see Key Secondary Endpoints 6.1.11.2

To assess robustness of study results, the primary endpoint ORR was also determined in the modified enrolled population (78 enrolled patients with an apheresis product accepted at the MP facility). For this analysis, patients with manufacturing failures are considered non-responders. For the modified enrolled population, the lower limit of the 95% exact Clopper-Pearson confidence intervals for ORR was above the null hypothesis rate (Table 13).

Reviewer Comment: The results of B2202 mirror results of single-agent therapies in newly-diagnosed patients with B-cell precursor ALL (Leiken, 1968) and exceeds the CR and CRp or CRh seen with the single agents clofarabine and blinatumomab respectively in relapsed/refractory pediatric B-cell precursor ALL population: 20% for clofarabine, 33% for blinatumomab. More importantly, the 63% CR is notable. The high CR rate, durability of CR, and MRD-negativity are sufficiently remarkable to warrant regular approval.

There remains lingering concern regarding the omission of restaging prior to start of lymphodepleting chemotherapy. However, it is fairly well-established that available treatment to date is not very effective for the pediatric patients with refractory ALL or after multiple relapses, so any remission achieved by the bridging chemotherapy is expected to be rare and very short.

Hence, it is concluded that the substantial CR rate observed here is due to the study therapy. It should be noted that this conclusion is particular to the circumstances and results of this study, and the expectation remains that future trials include an assessment of disease status after intervening therapy and prior to start of study therapy.

6.1.11.2 Analyses of Secondary Endpoints

Key Secondary Endpoint:

Minimal Residual Disease (MRD)
All of the responders were MRD negative in their bone marrows (Day 28) at the time their responses were documented.

Reviewer Comment: Source Data Set B1 and eCRF, confirmed by FDA reviewer. These efficacy results for the primary analysis and the key secondary analysis will be in section 14 of the tisagenlecleucel label.

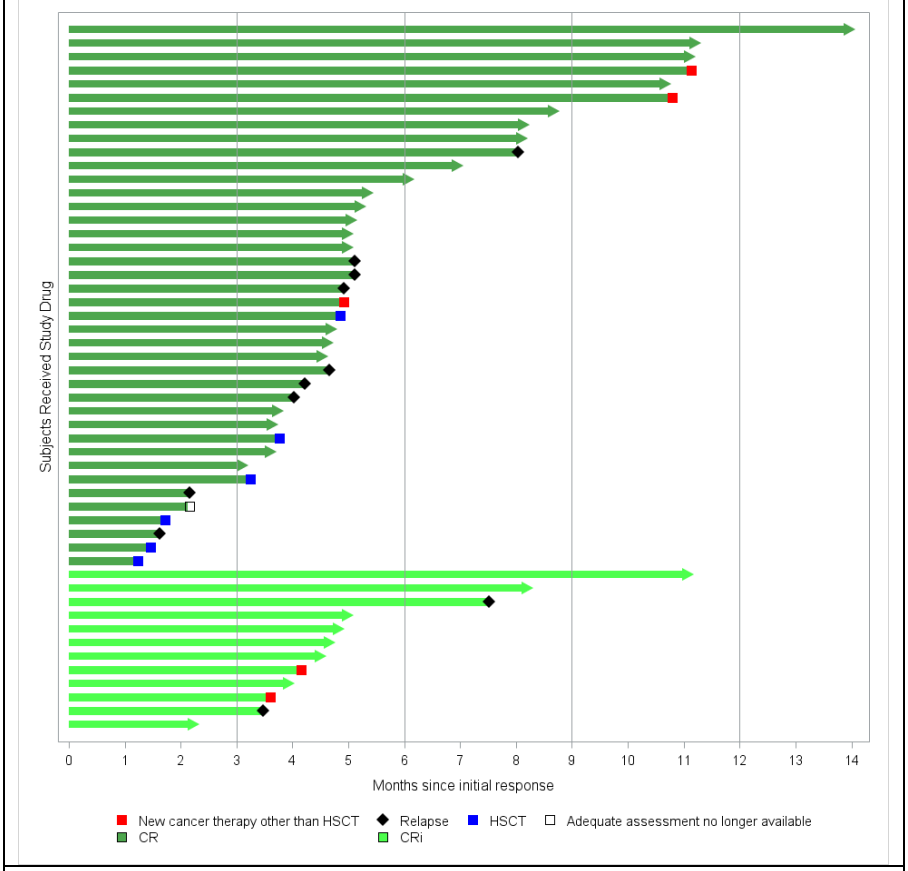
Other Secondary Endpoints:

Duration of remission (DOR) (provided by the FDA statistician)
In Study B2202, 11 of the 52 patients who achieved a CR+ CRi relapsed after tisagenlecleucel prior to the data cut-off date and before any new cancer therapy. In addition, two more patients relapsed after receiving both tisagenlecleucel and new cancer therapy. Twenty-nine of the 52 patients were still in remission at the last assessment before the data cutoff.

Twelve of the 52 patients were censored for DOR as follows: 6 patients for SCT, 5 patients for new cancer therapy, and 1 patient for adequate assessment no longer available. Four deaths occurred among responders; 3 of these deaths occurred after disease relapse. One new cancer therapy was initiated while in remission resulting in death. DOR was censored at the last adequate disease assessment before the initiation of the new cancer therapy; therefore the death was not a competing risk for relapse. In the absence of non-relapse mortality, a competing risk analysis was not conducted. Instead, the Kaplan-Meier analysis was used to analyze DOR.

The median follow-up time for DOR was 4.8 months. The median DOR was not reached (range: 1.2 – 14.1+ months). The estimated relapse-free rate among responders at Month 6 was 75.4% (95% CI: 57.2, 86.7). Figure 2 shows the swimmer's plot for DOR.

Figure 2: Duration of Remission



Source: FDA Statistical Reviewer

Review Comment: The swimmer's plot affirms that the patients can achieve a sustained remission.

Overall Survival (provided by the FDA statistician)
Eleven patients (17.5%) died after tisagenlecleucel infusion. No deaths occurred primarily from CRS. However, two patients died with symptoms of CRS, one with rapidly progressive disease (b) (6) and rising tisagenlecleucel cells and IL-6 and the second (b) (6) with decreased symptoms of CRS but with persistent coagulopathy post-surgery for abdominal compartment syndrome, receiving renal dialysis, and thrombocytopenic.

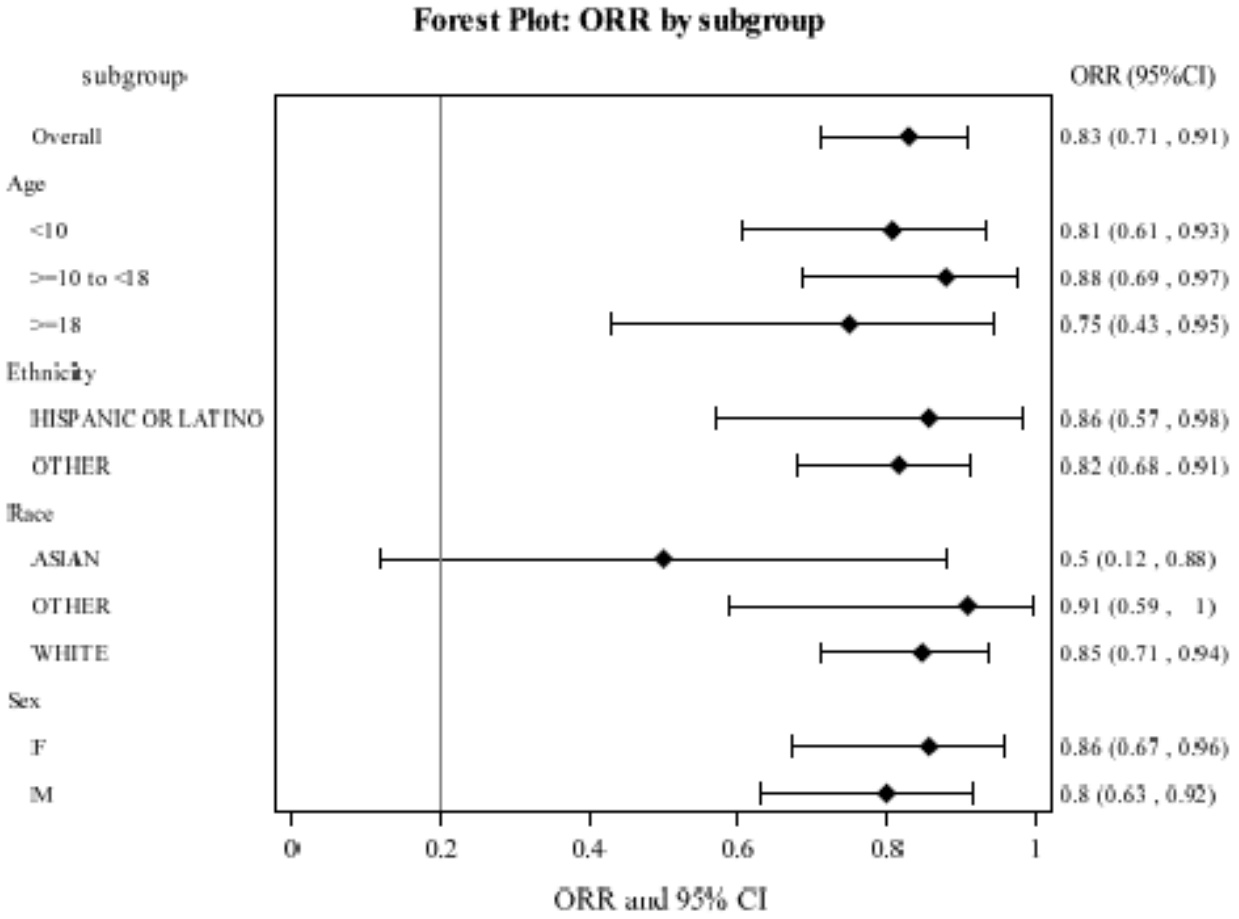
The median follow-up time for OS was 6.9 months (min=9 days, max=17.7 months). Median OS was 16.7 months (95% CI: 16.7, NE). The estimated survival rate at 6 months was 88.4% (95% CI: 77.0, 94.3) and at 12 months was 78.9% (95% CI: 63.0, 88.6).

Reviewer Comment: The length of follow-up for OS is short, so the estimates may not be reliable. Therefore, formal presentation of OS curves will not be included in the label. We will detail the deaths post-tisagenlecleucel and other reasons for patients off study in section 6 and 14 of the label.

6.1.11.3 Subpopulation Analyses

As stated previously, the B2202 efficacy analysis population was small (n=63). The figure below is a Forest plot performed by the FDA statistical reviewer with ORR analyses of subgroups defined by the demographics of the B2202 patients, i.e., age group, ethnicity, race and sex. Results of ORR are consistent among subgroups with one exception. There is less of an ORR in the Asian category for race, even though they exceeded the primary endpoint.

Figure 3: Forest Plot – ORR by demographic subgroups in Study B2202

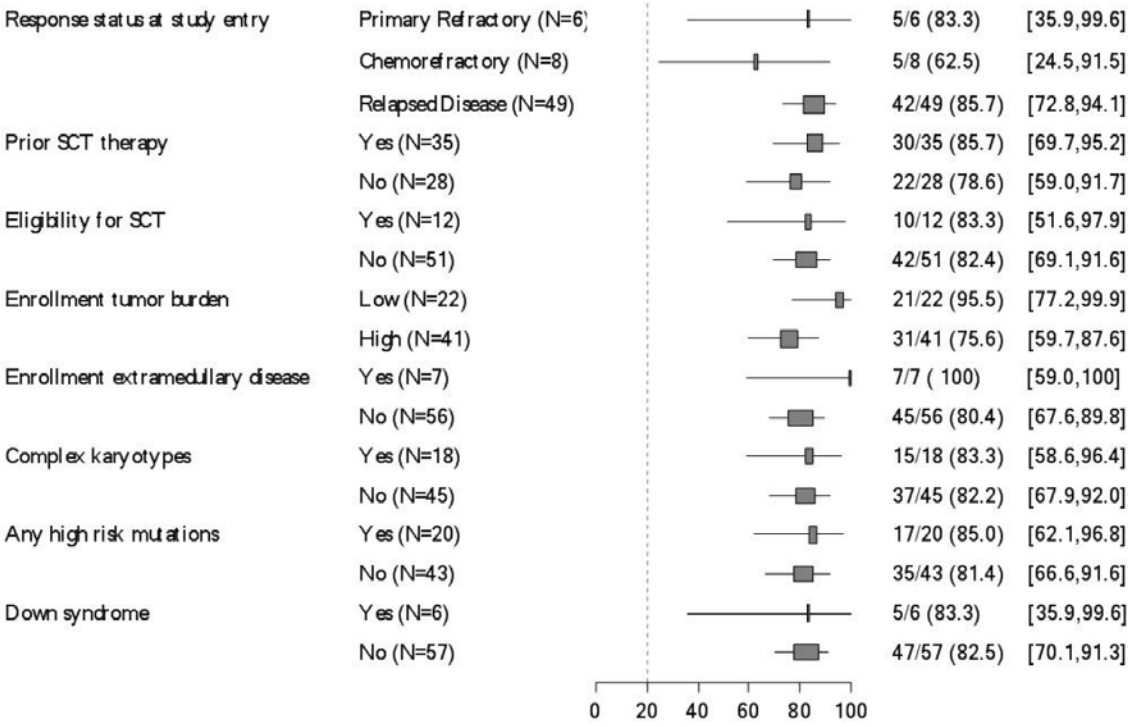


Source: FDA statistical reviewer's analysis, SAS dataset ADSL

Reviewer Comment: With the small numbers, the results are exploratory and will require further analysis when more patients receive tisagenlecleucel.

In addition to the above analysis, risk parameters such as disease burden, cytogenetic abnormalities, refractory versus relapsed, were also evaluated by the Applicant. Those results are show in Figure 4.

Figure 4: Forest Plot for IRC – assessed ORR by subgroups in Study B2202



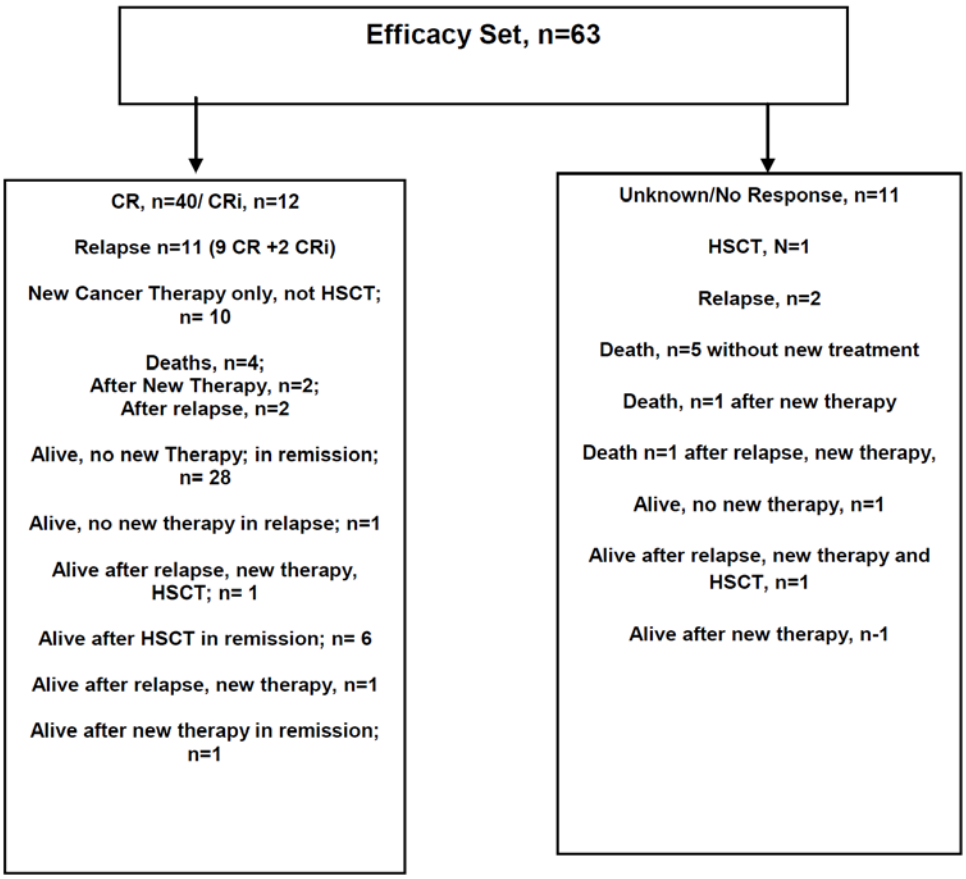
Source: BLA: SCE Addendum 1-Appendix 2-Figure 3-5.1
CI: confidence interval, IRC: independent review committee, ORR: overall remission rate; SCT: stem cell transplantation.

Reviewer Comment: Since the number of treated patients is small, this is an exploratory assessment. However, all of the subgroups exceeded the predicted primary endpoint assessment. Further study will be needed with tisagenlecleucel therapy to determine if there is predictive value to these common high risk features. In future studies, disease assessment immediately prior to the tisagenlecleucel infusion would further delineate the role of tumor burden on response and the severity of adverse reactions such as cytokine release syndrome, neurologic toxicities, and other safety reactions.

6.1.11.4 Dropouts and/or Discontinuations

The outcomes for patients in the Efficacy Population.at the data cut-off are shown in Figure 5 .

Figure 5: Outcome of the Efficacy Set



Source: FDA Reviewer

Reviewer Comment: This is the outcome of the efficacy population. Among the unknown responses there were protocol deviations that did not permit adequate assessment of the patient. One patient who went to HSCT did so immediately after the day 28 evaluation and therefore did not have confirmation of complete remission. One patient (alive in remission at 5 months) never had a cerebrospinal assessment required to confirm remission. There were 2 deaths in remission before day 30 and one death due to an AE before confirmation of a response. One responder dropped out of primary follow-up after 3 months due to the distance from the primary treatment site.

6.1.11.5 Exploratory and Post Hoc Analyses

Post hoc Assessment of CRh

FDA also conducted an exploratory post hoc analysis to determine how many of the patients with CRi actually achieved complete remission with partial hematological recovery (CRh). The criteria for CRh include <5% marrow blasts, ANC > 0.5 x 10^9/L and platelets > 50 x 10^9/L but not reaching ANC or platelet counts needed for CR. Of the 12 patients with CRi, 9 fulfilled the criteria for CRh. Overall, 49 patients (78%) achieved CR or CRh.

Post hoc Assessment of CR/CRi in patients who did not receive LD chemotherapy.

Three patients in the safety population did not receive LD chemotherapy; all had WBC < 1 x 10^9/L. Two of those patients were in the efficacy population. For the efficacy population, that was one CR and one unknown (early death, incomplete evaluation). The last patient was in the Safety population and an unknown in the Day 60 Safety update – per the CRFs the day 28 BM was CR but no confirmation by the IRC.

6.1.12 Safety Analyses

6.1.12.1 Methods

This Safety Analysis Population included the 68 patients who received tisagenlecleucel before the data cut-off of November 23, 2016. This included product manufactured in Morris Plains, New Jersey (n=63) and at the Fraunhofer Institute in Germany (n=5) who were treated on B2202. In addition, adverse event and deaths were also assessed for the period from enrollment to the planned time of infusion for patients (n=88) to assess risks for patients who were eligible to receive tisagenlecleucel but were not infused due to manufacturing issues or adverse events.

Monitoring for Adverse Events
Adverse event reporting pre-infusion with tisagenlecleucel, starting at consent, was limited to all events leading to death, pulmonary and cardiac events, infections, events related to study procedure, if an AE was considered serious, any change in status of the patient which precluded lymphodepletion or treatment with tisagenlecleucel.
After tisagenlecleucel infusion, follow-up evaluations were to be performed as detailed in Table 33 Appendix B.

After day 28, patients were monitored monthly through month 6 for adverse events, then every 3 months for 2 years, then every 6 months until month 60. Per (Table 33), Patients were evaluated for retrovirus competent replication (RCR) and persistence of the tisagenlecleucel cells to assess risk for secondary malignancy starting at month 3 and the every 3 months for the first year and then every 6 months. Once negative for two samples, subsequent blood samples were stored for reference.

Adverse Events (AEs) and serious adverse events (SAEs) were evaluated during clinic visits, hospitalizations, and follow-up clinic visits per protocol defined guidelines. Safety evaluations were performed for 12 months after infusion and included: vital signs, clinical hematology laboratory testing, clinical chemistry laboratory testing, coagulation laboratory testing, and lumbar punctures. Cardiac monitoring with echocardiograms, EKGs; and clinical neurologic evaluations were done at baseline as well as pre-infusion. In addition, as needed by the clinical status of the patients, CT, and MRI evaluations, which were not mandated at baseline, were done based on clinical presentation After tisagenlecleucel infusion, all adverse events were recorded and reported Table 33 Appendix B.

Long-Term Follow-Up For tisagenlecleucel
For the first five years, assessment for second malignancy, persistence of tisagenlecleucel cells and RCR are done on B2202. After 60 months, this follow-up is done on a separate long-term follow-up protocol A2205B.

Adverse Event Grading Systems
AEs were graded as CTCAEv4.03 Grade 1 through 5, with Grade 5 being death. CRS grading was an exception. The UPenn Grading system was used to evaluate CRS and is detailed in Table 32 Appendix A . The duration of safety follow-up was one year.
MedDRA terms were used to identify safety issues and included in the datasets.

Safety data were organized into pre and post-tisagenlecleucel groupings. Safety data in the or the pre-infusion group, was analyzed further based on the period from apheresis to lymphodepletion and lymphodepletion to infusion of tisagenlecleucel. Post-tisagenlecleucel safety data was analyzed further, from infusion to 8 weeks post-tisagenlecleucel and from > 8 weeks to one year.

Serious adverse events were defined per 21 CFR 312.32

6.1.12.2 Overview of Adverse Events

Pre-tisagenlecleucel and Lymphodepletion (LD) Adverse Events

Table 14: Selected Pre-Infusion and LD Adverse Events (≥ 5%)

Body System Or Organ Class	Dictionary Derived Term	Pre-treatment period N=88 (%)	Pre-treatment period N=88 (%) Grade ≥ 3	Lympho-depleting period (LD) N=68 Received LD n=65	Lympho-depleting period (LD) N=68 Grade ≥ 3
Patients with events		**79 (90%)**	**75 (85%)**	**52 (76%)**	**24 (35%)**
Blood And Lymphatic System Disorders	**Febrile Neutropenia**	**21 (24%)**	**21 (24%)**	**3 (4%)**	**3 (4%)**
Cardiac Disorders	**Tachycardia**	**7 (8%)**	**3 (3%)**	**2 (3%)**	**0**
General Disorders And Administration Site Conditions	**Fatigue**	**5 (6%)**	**0**	**1 (1%)**	**0**
	Pain	**5 (6%)**	**0**	**0**	**0**
	Pyrexia	**15 (17%)**	**2 (2%)**	**6 (9%)**	**0**
Infections And Infestations		**47 (53%)**	**43 (49%)**	**9 (13%)**	**5 (7%)**
Vascular Disorders	**Hypertension**	**6 (7%)**	**0**	**0**	**0**
	Hypotension	**6 (7%)**	**5 (6%)**	**4 (6%)**	**1 (1%)**

Source: ADSL Enrolled Flag; ADAE

There were 88 patients at the start of the pre-treatment phase, and only 68 were qualified to proceed to the lymphodepletion phase. Of the 20 patients who did not proceed to tisagenlecleucel infusion, there were 4 awaiting infusion, 3 adverse events preventing infusion, 7 manufacturing failures, one death and manufacturing failure, and 6 deaths (Figure 1 and Table 10). Of the 68 who entered the LD phase of pre-therapy, all received tisagenlecleucel with or without LD. There were 65 patients who received LD and tisagenlecleucel. Three of 23 patients with WBC less than 1 x 10^9/L did not receive LD per protocol. There were overlapping toxicities among patients.

Reviewer Comment: The issue of pre-tisagenlecleucel safety evaluation is important in the context of this heavily pretreated population. This relates to the medical status of patients who should or should not receive tisagenlecleucel. In addition, it provides information for the product label. This information will outline the medical conditions that would preclude a patient from

receiving tisagenlecleucel such as an ongoing and active infection(s) or exacerbation of their ALL. Per protocol, there was an interval between bridging chemotherapy and LD. Therefore, AEs were reported separately.

Post-tisagenlecleucel Adverse Events

Table 15: Selected Adverse Events (≥ 10%): Safety Population: Post-tisagenlecleucel

Body System or Organ Class	Dictionary Derived Term	Post-tisagenlecleucel period n (%)	Grade 3 or Higher n (%)
Patients		68 (100%)	57 (84%)
Blood And Lymphatic System Disorders	Anemia	21 (31%)	9 (13%)
	Febrile Neutropenia	26 (38%)	26 (38%)
Cardiac Disorders	Tachycardia	17 (25%)	3 (4%)
Gastrointestinal Disorders	Abdominal Pain	10 (15%)	2 (3%)
	Vomiting	18 (26%)	1 (1%)
General Disorders And Administration Site Conditions	Chills	7 (10%)	0
	Fatigue	15 (22%)	0
	Fever	27 (40%)	10 (15%)
Immune System Disorders	Cytokine Release Syndrome	54 (79%)	33 (49%)
	Hypogammaglobulinemia	20 (29%)	3 (4%)
Infections And Infestations		40 (59%)	19 (27%)
	Fungal Infectious Disorders	9 (13%)	5 (7%)
Metabolism And Nutrition Disorders	Decreased Appetite	25 (37%)	10 (15%)
	Fluid Overload	7 (10%)	5
Musculoskeletal And Connective Tissue Disorders	Arthralgia	8 (12%)	1 (1%)
	Back Pain	7 (10%)	2 (3%)
	Myalgia	10 (15%)	0
	Pain In Extremity	11 (16%)	1 (1%)
Nervous System Disorders	Encephalopathy	8 (12%)	4 (6%)
	Headache	24 (35%)	2 (3%)
Psychiatric Disorders	Agitation	6 (9%)	0
	Anxiety	9 (13%)	2 (3%)
	Confusional State	7 (10%)	0
	Delirium	7 (10 %)	3 (4%)
Renal And Urinary Disorders	Acute Kidney Injury	14 (21%)	8 (12%)
Respiratory, Thoracic And Mediastinal Disorders	Cough	13 (19%)	0
	Hypoxia	16 (24%)	12 (18%)
	Nasal Congestion	7 (10%)	0
	Pleural Effusion	7 (10%)	3 (4%)
	Pulmonary Edema	11 (16%)	7 (10%)
	Tachypnea	8 (12%)	4 (6%)
Vascular Disorders	Hypertension	13 (19%)	4 (6%)
	Hypotension	21 (31%)	15 (22%)

Source: ADSL ADAE JReview

Laboratory and metabolic events related to elevated or decreased chemistries will be discussed in section 6.1.12.6. All patients experienced at least one adverse event and 84% experienced a Grade 3 or higher event. There were overlapping events in the same patient.

Reviewer Comment: It was not uncommon for the patients within the restrictions of the eligibility criteria to enter the study with pre-existing medical conditions. In addition, 58% received bridging chemotherapy for leukemia control after apheresis which was followed by cyclophosphamide and fludarabine as lymphodepletion for tisagenlecleucel in 96% of the patients. The events represented above reflect not only the toxicities of tisagenlecleucel but prior therapies, such as the recent bridging chemotherapy and LD. Close monitoring for adverse events is crucial for the safe administration of tisagenlecleucel.

6.1.12.3 Deaths

Overall, 29 deaths have been reported from time of informed consent to the data cut-off of the study (November 23, 2016) as submitted for the BLA. To be screened, one had to sign an informed consent. Table 16 provides details of enrolled patients; that is patients who successfully completed screening but then died on the trial and those who died after tisagenlecleucel respectively. Among patients who failed screening (not included in Table 16), there were six deaths: two patients died during screening, 2 patients died from ALL, one died due to a colonic hemorrhage, and one died due to a fungal infection.

Table 16: Pre-Infusion Deaths with Cause (n= 12)

Death Primary Reason	Death Primary Reason Preferred Term	Unique Subject Identifier	N=88 n
Other	Fungemia	CCTL019B2202 (b) (6)	1
	Pneumonia	CCTL019B2202	1
	Pneumonia Fungal	CCTL019B2202	1
	Pneumonia Klebsiella	CCTL019B2202	1
	Respiratory Failure	CCTL019B2202	1
	Sepsis	CCTL019B2202	1
Study Indication	Acute Lymphocytic Leukaemia	CCTL019B2202	1
		CCTL019B2202	1
		CCTL019B2202	1
		CCTL019B2202	1
		CCTL019B2202	1
		CCTL019B2202	1

Source: ADSL JReview

Reviewer Comment: As noted above not all patients can expect to proceed to tisagenlecleucel infusion after the successful pheresis for the manufacture of tisagenlecleucel. In the enrolled population there was a 14% chance of death in the manufacturing phase. Patients will need to

be informed that during the manufacturing period in the relapsed and refractory clinical setting, that there is also a risk of progression of their ALL, severe adverse events from bridging chemotherapy, and/or lymphodepleting chemotherapy. Unfortunately, for this R/R ALL population, these events are not unusual. In addition, not all manufacture of the tisagenlecleucel is successful, there is up to a 9% failure rate.

Table 17: Deaths Post-tisagenlecleucel (n=11)

Death Primary Reason	Death Period	Secondary Cause of Death	N=68 N (%)
Infection	**Death >30 days after tisagenlecleucel infusion**	**Encephalitis** **Lower Respiratory Tract Infection (Bacterial)** **Systemic Mycosis**	**3 (4%)**
Cerebral Hemorrhage	**Death within 30 days of tisagenlecleucel infusion**	**Cytokine Release Syndrome**	**1 (1%)**
Acute Lymphoblastic Leukemia	**Death >30 days after tisagenlecleucel infusion**	**None**	**6 (9%)**
	Death within 30 days of tisagenlecleucel infusion	**Cytokine Release Syndrome**	**1 (1%)**

Source: ADSL, JReview

Death Narratives for deaths post-tisagenlecleucel:
Two deaths within 30 days

- Recurrent ALL
  - B2202-(b) (6)
    - 11 yo girl
    - on broad spectrum antibiotics, antivirals, antifungal immediately prior to infusion In leukemia relapse, prior to infusion of tisagenlecleucel characterized by fever, organomegaly, elevated calcium, coagulopathy, elevated CRP, and bilirubin. LD improved symptoms
    - Fever, hypercalcemia, and hypertension start on Day 6 (5 days post-tisagenlecleucel).Given O2, fluids.
    - Peripheral blasts noted 7 days after infusion
    - Given Zoledronate and denosumab for calcium mitigation.
    - Symptoms mimic cytokine release syndrome, treated with tocilizumab
      - Elevated levels of tisagenlecleucel cells and IL-6
      - When these levels are compared to the 4 non-responders, all of whom were reported to have CRS (Grades 1-4); this index case had lower expansion of tisagenlecleucel cells and lower levels of IFNγ. The IL-6 levels were higher than 3 of the 4 and similar to one.
      - Given tocilizumab 10 days after infusion.
    - Progression of ALL, organomegaly, hypercalcemia, MRD 28% CD19+ leukemia cells. ECHO shows massive liver and periportal infiltration, ascites but no clot.
    - At autopsy CBC 64% blasts.

- Death due to ALL and late CRS; starting (b) (6) days after tisagenlecleucel

- Intracranial Hemorrhage
  - B2202-(b) (6)
    - 6 yo boy
    - Down Syndrome
    - CRS Grade 4 recovering but still on dialysis on Day 12 for Grade 4 kidney injury
    - Two days post-abdominal surgery for compartment syndrome on Day 13
    - Grade 2 disseminated intravascular coagulation (treated with cryoprecipitate and Vitamin K. Thrombocytopenia.
    - Off pressors and developed hypertension
    - Intracranial hemorrhage on Day (b) (6) fatal.

<u>9 deaths after 30 days</u>

- 6 from progressive/recurrent ALL
  - 5/6 experienced Grade 1-4 CRS
  - secondary peaks of tisagenlecleucel seen in 2/6
  - IL-6 values were increased over baseline
- 1 encephalitis
  - B2202 -(b) (6)
    - 4 year-old girl with primary refractory ALL.
    - Initially Grade 4 CRS that responded slowly to therapy
    - Neurologic toxicity including Grade 3 encephalopathy
    - Persistent pancytopenia
    - 34 days after tisagenlecleucel, cerebral spinal fluid positive for HHV6B
    - Died on Day (b) (6) due to encephalitis; ALL in remission
- 1 respiratory tract infection (bacterial)
  - B2202-(b) (6)
    - 16 year-old boy
    - Infused May 12, 2015
    - Off protocol for new therapy for ALL
    - (b) (6) , died due to bacterial lung infection
    - 1 systemic mycosis
- 1 Infection
  - B2202-(b) (6)
    - 18 year-old girl with relapsed ALL
    - April, 28, 2016, received 2 x 10e8 tisagenlecleucel cells
    - April 29, 2016: stomatitis (Grade 2), ulcerative gingivitis (Grade 3), and oral candidiasis (Grade 1)
    - May 13, 2016: 15 days after infusion, Candida guilliermondii-positive blood culture
    - May 25, 2016: Grade 4 Candida, fever, increased respiratory symptoms
    - (b) (6) , died with known sinusitis, oral herpes simplex, HHV6, pancytopenia, and systemic Candida

Twenty-nine of 107 screened patients died during the course of the study. Six in the failed screened population, 12 pre-infusion and 11 post-tisagenlecleucel. Fifteen were disease-related.

Reviewer Comment: No deaths were attributed to cytokine release syndrome by the applicant. However, as noted in the two early deaths, one was experiencing symptoms of CRS while progression of leukemia occurred and the second death occurred as CRS was resolving due to an intracranial hemorrhage (ICH) due to a CRS related coagulopathy. The patient with the progressive disease (Patient ID (b) (6) *prior to 30 days also was experiencing symptoms of CRS. Comparison with the other 4 patients with no response shows that they all had the clinical presentation of CRS but three of four had lower levels of IL-6. Given the clinical picture, the fact that the other 4 non-responders had CRS while experiencing recurrence, CRS cannot be ruled out as a partial cause of death in this patient. In the patient with the ICH Patient ID* (b) (6) *, CRS was a secondary cause of death. Looking at the early relapsed patients, 5/6 with CRS, there is no pattern to cell expansion or increase in IL-6. While* (b) (6) *did experience an increase in both tisagenlecleucel cells and IL-6, it is not enough to make a definitive diagnosis. Reviewing the clinical report on the CRF form, CRS cannot be ruled out, the patient had an elevated temperature, hypotension, and respiratory compromise.*

The patient population for B2202 was fragile. The patients had an average prior exposure to multi-agent chemotherapy of three regimens and 59% were post-failed HSCT. Prior therapies, pre-existing conditions, and increased risk of infection contributed to the deaths prior to infusion. Despite eligibility criteria to assure recovery from prior therapies, the patients had poor tolerance for medical complications. This information will need to be conveyed to the patients in the label. This also justifies the requirement for the REMS with ETASU. The applicant had a site and investigator training program in place during the IND phase as well as close follow-up of all adverse events. To assure safety in the commercial setting, we are requiring that site who will administer tisagenlecleucel will have site and investigator training. See Section 4.6.

6.1.12.4 Nonfatal Serious Adverse Events

Serious adverse events occurred after tisagenlecleucel

Considering the fact that all patients entered the trial in relapse, most received chemotherapy (85% in the safety population) and/or LD (96%) prior to the tisagenlecleucel and 79% experienced CRS. A detailed discussion of some of the adverse events is available in the AE section and in the Adverse Events of Special Interest section. All patients experienced at least one adverse event and 57 (84%) had Grade 3 or higher adverse events.

Table 18 Serious Adverse Events: SOC Preferred Term > 5%

Body System	Preferred Term	Post-tisagenlecleucel period N=68	Grade 3 or Greater
Blood And Lymphatic System Disorders	**Febrile Neutropenia**	**14 (21%)**	**14 (21%)**
General Disorders And Administration Site Conditions	**Pyrexia**	**5 (7%)**	**1 (1%)**
Immune System Disorders	**Cytokine Release Syndrome**	**43 (63%)**	**31 (45%)**
Renal And Urinary Disorders	**Acute Kidney Injury Renal Failure Renal Tubular Necrosis**	**7 (10%)**	**7 (10%)**
Vascular Disorders	**Hypotension**	**8 (12%)**	**8 (12%)**

Source: ADSL, ADAE

Reviewer Comment: The assessment of the SAE Table 18 has to be in the context of the reality of the seriousness of most of the AEs experience by the patients who receive tisagenlecleucel based on predesignated criteria for serious adverse events. In the context of the safety review for tisagenlecleucel, the incidence of adverse events Grade 3 or higher or Adverse events of special interest provide a much more distinct model for the safety profile of tisagenlecleucel. The discrepancy between serious AE rates and Grade 3 or greater AEs does not provide an accurate safety profile. The reviewer recommends a focus on AEs of greater than or equal to Grade 3 and the AESI to assess safety.

6.1.12.5 Adverse Events of Special Interest (AESI)

The applicant identified adverse events of special interest which were important in the context of management of the clinical syndrome of CRS and assessment of risks in the post-tisagenlecleucel phase of the study. Adverse events of Special Interest for safety analyses included febrile neutropenia, CRS, infection, transient neuropsychiatric events, cytopenias lasting greater than 28 days. CRS for safety analyses was a single term per the applicant. However, the symptoms followed for the diagnosis on the eCRF were fever, ICU status, hypotension, dyspnea, tachypnea, hypoxia, organ failure (intubation, dialysis), and acute respiratory symptoms.
The applicant's analysis for neurotoxicity did not include all neurotoxicity, but focused on serious neurotoxicity events related to encephalopathy, delirium, focal deficits, and seizures. Applicant used the MedDRA SMQ Broad for noninfectious encephalitis.

Table 19: Adverse Events of Special Interest Post-tisagenlecleucel

Study B2202 N=68	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
CRS	**14 (21)**	**19 (28)**	**54(79)**
Transient neurologic events	**12 (18)**	**0**	**44 (65)**
Febrile Neutropenia	**24 (35)**	**2 (3)**	**26 (38)**
Hematopoietic cytopenia not resolved by Day 28	**13(19)**	**12 (18)**	**36 (53)**
Infections	**17(24)**	**2 (3)**	**40 (59)**

Source: FDA analysis ADSL, ADAE, ADAERISK

For the purpose of this review, the FDA has grouped the definition of transient neurologic (neuro-psychiatric) events into categories and the adverse events of special interest have been modified. For example, the applicant chose the MAED SMQ_B Non-infectious encephalopathy/delirium to define neuro-psychiatric events. As a result, the applicant choose to exclude headaches. This reviewer has added them and this increases the incidence of neurologic adverse events. While headache may be non-specific, in this population, it is uncommon and may be clinically relevant. Please note that one patient as previously discussed suffered an intracranial hemorrhage Grade 5 which is not included in neurologic events as measured by the FDA.

Reviewer Comments: The purpose of a review of AESI is to highlight events that occur and need to be effectively treated or mitigated to allow for the safe infusion of tisagenlecleucel. There are several categories of AESI. CRS and neurologic events are serious adverse events but extensive supportive care is needed to assure the safety of the patient while they are experiencing the events. The REMS will address both. The REMS will educate the health-care

providers on the pathophysiology of both and the appropriate treatment algorithm for CRS (including the use of tocilizumab) and the supportive care needed for neurologic toxicities.

Infusion related reactions
Four infusion related reactions were recorded (Grade 1 or 2). None were recorded on the day of the tisagenlecleucel infusion.

Reviewer Comment: There is DMSO in the product so the risk of an infusion related reaction exists which should be conveyed to healthcare providers in the label as well as the training materials for the REMS Elements to Assure Safe Use (ETASU).

Cytokine Release Syndrome:
For purposes of the evaluation of CRS, the applicant used the UPenn Grading Criteria please refer to APPENDIX A (Porter, 2015). This grading criterion was based on clinical symptoms, the need and type of intervention. For example, Grade 2 was defined as CRS symptoms that required hospitalization and/or need for intravenous therapies and management of CRS related symptoms and neutropenia.
On Study B2202, 54 of 68 (79%) patients treated with tisagenlecleucel (Table 19) experienced CRS. 33/68 (49%) of patients had Grade 3/4 CRS.

- CRS onset occurred at a median of 3 days, with a range of 1-22 days.
- CRS Grade 3/4 onset occurred within 6 days; the median duration of Grade 3 /4 CRS was 9 days (3 -28).
- Median duration of all grades of CRS was 8 days (range 1 to 36).
- With the exception of the two deaths, all patients recovered from CRS. There were some sequelae as noted in the cardiac section below.

Serious morbidities associated with CRS (n=54, percentages based on n=68 for safety population). These results came from review of the CRS specific report forms as well as AE reports:

- Eight patients required dialysis on B2202 with CRS; all but one of the patients who were dialyzed had elevated creatinine at Grade 1-3.
- There was no correlation between the dose of tisagenlecleucel cells and the grade of CRS.
- Infections, as described in the case report forms for CRS, occurred in 12 patients during CRS; these infections included one pneumonia, one typhlitis, 6 episodes of bacterial sepsis, one viral encephalitis. Multiple positive cultures in one patient occurred.
- Fifty patients had fevers, with a median duration of 6 days and a range of 1-36 days.
- Thirty-two Study B2202 patients with severe CRS were admitted to the ICU, with a median ICU stay of 6.5 days (range 1-34 days).
- Eleven patients required ventilatory support with intubation for a median of 6 days (range 1 - 19 days)
- 36 patients had documented hypotension
- During CRS, 12 patients developed disseminated intravascular coagulation (DIC). There were 9 reports of bleeding, 4 in patients with DIC (2 gastrointestinal, mucous membranes, and ICH) and 5 with no DIC reported (2 mucous membranes, 1 hematuria, 1 IV lines, and 1 pulmonary).
- Concurrent CRS with Grade 3 neurotoxicity was noted. (11/12 patients) see Table 23 below (encephalopathy, delirium, seizure).

- In the Study B2202 patients, tumor burden was assessed at baseline evaluation (before bridging and lymphodepletion) as low < 50% (n=23) versus high ≥ 50% (n=45) BM involvement. Seventeen patients with low tumor burden developed CRS; 6 developed Grade 3 or 4. Thirty-seven patients with high tumor burden developed CRS, 33 developed Grade 3 or 4 CRS. There was a trend toward correlation between tumor burden and severity of CRS. (Table 21)
- The occurrence of CRS did not correlate with ORR. In fact, 4 non-responders experienced CRS.

Reviewer Comment:
The infections noted above reflect those recorded directly on the specific CRF case report forms and are not inclusive on all of the infections that occurred in these patients after tisagenlecleucel. The nature of the infections is notable. They are similar to those reported after allogeneic stem cell transplantation. Patients experienced bacterial sepsis but also there were reports of systemic fungal infections and reactivation of viral infections (HHV-6 and CMV).

In the Safety Analysis Population, 27 patients received tocilizumab for the management of CRS.

Table 20 Tocilizumab

	n (%)
Systemic Anticytokine given [n (%)] n=54 with CRS	27(50)
Tocilizumab • 1 dose • 2 doses • 3 doses	 17 (31) 7 (13) 3 (6)

Source: ADSL, ADLB, JReview

Reviewer Comment: In the REMS ETASU, the FDA is requiring that sites have two doses of tocilizumab for each patient at the center prior to the infusion of tisagenlecleucel. The above tally for the usage of tocilizumab justifies this request. The majority of the patients responded to one or two doses.

In our assessment of the use of tocilizumab in patients with Grade 3 CRS we noted that fourteen patients experienced Grade 3 CRS but only 7 were treated with tocilizumab. Of the 7 who received tocilizumab, the median duration of CRS was10 days (range 7 – 22 days), median time in ICU was 3 days (range 1 – 14 days) and for those who did not receive tocilizumab, the median duration of CRS was 7.5 days (range 4 – 36 days) and the median time in the ICU was 3.5 days (range 0 – 6 days). Comparing the treated to the untreated with the CRS algorithm in use for the IND and planned for the commercial setting, confirmed that the algorithm recommendations were followed. The clinical symptoms of CRS reflect the number of tisagenlecleucel cells present. We note that all Grade 4 CRS patients received tocilizumab.

Reviewer Comment: The use of tocilizumab is based on symptoms. Hemodynamic instability despite intravenous fluids, moderate to "high dose" vasopressor support or worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow Oxygen (O2) and/or need for mechanical ventilation or rapid clinical deterioration are the recommended indications for tocilizumab. When you look at the Grade 3 treated versus non-

treated, those with the symptoms that required tocilizumab were treated. The duration of CRS is longer but they were more symptomatic than those who were not treated because the algorithm required patients with more severe CRS to receive tocilizumab (refer to Table 28*).*

Table 21 Cytokine Release Syndrome and Tumor Burden					
Safety Population n=68					
Baseline bone marrow tumor burden	**GRADE 1 CRS**	**GRADE 2 CRS**	**GRADE 3 CRS**	**GRADE 4 CRS**	**Total with CRS**
High (≥ 50%)	**2**	**8**	**12**	**15**	**37**
Low (< 50%)	**3**	**8**	**2**	**4**	**17**
Patients	**5**	**16**	**14**	**19**	**54**

Source: ADAERISK, ADSL, JReview

Greater than 50% involvement in the BM at screening did increase the incidence and severity of CRS in the patients on B2202 with CRS.

Reviewer Comment: This data analysis is based on tumor burden at screening before patients received bridging chemotherapy (85%) and LD (96%). The appropriate time for measurement of tumor burden would have been before the infusion of tisagenlecleucel and after these therapies. However, the data from screening does reflect that there is a trend toward more severe CRS with higher tumor burden and therefore should be included in the label.

Other interventions for CRS:

Table 22: CRS Additional Therapies

B2202 CRS Additional Therapy	**N=54 (%)**
Corticosteroids	**14 (26)**
Siltuximab	**5 (9)**
Other	**2 (2)**
CRS All Grades	**54**

Source: ADCM JReview

The use of siltuximab post-tocilizumab and the effect is difficult to assess in such as small sample size. CRS resolved in the 4 of 5 patients who survived in 3 to 11 days after siltuximab was given (median 3.5). The use of corticosteroids is more difficult to assess. Corticosteroids were given before any tocilizumab, with tocilizumab and/or siltuximab, or after tocilizumab.

Reviewer Comment: Cytokine release syndrome is a serious condition that was experienced by 79% of the recipients of tisagenlecleucel who are treated for R/R ALL under the IND. Thus, the incidence and severity of CRS, predictive factors for CRS (such as tumor burden), the life-threatening nature, and associated comorbidities that require intense monitoring and supportive care measures warrant risk mitigation. In the IND phase, the sponsor certified sites, preferably choosing pediatric transplantation centers, trained healthcare professionals at the sites, and closely monitored sites for adverse events and compliance with the CRS treatment algorithm. The postmarketing considerations for the BLA include an observational study that will report AEs to the applicant. The FDA is also requiring a Risk Evaluation and Mitigation Strategy (REMS) with Elements To Assure Safe Use to minimize risk to patients which is justified by the severity of the adverse events experienced by the patients on the B2202 and the effective risk mitigation by the sponsor for these patients. The REMS ETASU that we are requiring will continue site and healthcare provider training with periodic assessments to assure that the recommendations and requirements of the REMS ETASU are being followed (Draft Guidance, 2016). Per section 505-1(f)(1), the FDA may require a REMS if a drug has been shown to be

effective but is associated with a serious adverse event. In this case that would be CRS and neurotoxicity. The ETASU will mitigate these specific risks which will be on the label. This decision was made due to the effectiveness of the risk mitigation procedures used by the applicant in the IND phase. We feel that the communication plan, label, and recommended assessments are not sufficient in this case to successfully assure the safety of the patients in the commercial setting. We have included in the ETASU recommendations, reviews of the progress at 6 months, and then yearly. The REMS is described in section 4.6.

The limited use of other agents for the treatment of CRS precludes a therapeutic judgment on their benefit. In general, siltuximab was given after tocilizumab but in the 4 surviving patients who received siltuximab, there is limited data to assess affect. For corticosteroids, they were given prior to, after or with tocilizumab over a short period of time to improve CRS. This makes it difficult to assess their effect.

Neurologic (Neuropsychiatric) Toxicity

Neurotoxicity was characterized by events related to encephalopathy, delirium, focal deficits, aphasia, and seizures. Neurotoxicity was reported by the applicant in 44% (n=30) of the patients who received tisagenlecleucel. The applicant analysis excluded headaches. Ten (15%) of those patients had Grade 3 neurotoxicity.

Below is the FDA review of neurologic toxicity which uses MedDRA system organ class for neurologic and psychiatric toxicity without intracranial hemorrhage. In our assessment, there were 44 (65%) patients with neurologic toxicities reported. There were 12 with Grade 3 (18%) and there were no Grade 4 events. The intracranial hemorrhage will be assessed with bleeding and was a Grade 5. This analysis added headaches which occurred in 31% (n=21). All of the Grade 3 events of neurotoxicity in the FDA analysis occurred within 8 weeks of tisagenlecleucel. Patients experienced more than one event. Some events carried over from the earlier time period of up to 8 weeks into the longer term reporting of up to a year; examples, insomnia and anxiety.

Table 23: Neurologic Events per FDA assessment

	Within 8 weeks post infusion All Grades	Within 8 weeks ≥ Grade 3	>8 weeks to 1 year post infusion*		Anytime<1year All Grades No Grade 3 after 8 weeks		Duration of Events (start < 8wks) Median (Days) (Range)
Group Term	**N (%)**	**N (%)**	**N**	**%**	**N**	**%**	
Encephalopathy	**22 (32%)**	**6 (9%)**	**2**	**3%**	**23**	**34%**	**3.5 (1 – 43)**
Headache	**21 (31%)**	**1 (1%)**	**9**	**13%**	**25**	**37%**	**4.5 (1 – 16)**
Delirium	**14 (21%)**	**3 (4%)**	**1**	**1%**	**14**	**21%**	**5.5 (1 – 30)**
Anxiety	**6 (9%)**	**2**	**3**	**4%**	**9**	**13%**	**10 (1-197)**
Tremor	**6 (9%)**	**0**	**0**	**0%**	**6**	**9%**	**5 (1 - 147)**
Dizziness	**3 (4%)**	**0**	**1**	**1%**	**4**	**6%**	**1 (1 – 69)**
Insomnia	**3 (4%)**	**0**	**1**	**1%**	**4**	**6%**	**52 (6 - 400)**
Dysgeusia	**3 (4%)**	**0**	**0**	**0%**	**3**	**4%**	**10 (1 - 48)**
Sleep Disorder	**2 (3%)**	**0**	**1**	**1%**	**3**	**4%**	**4 (2 – 13)**
Dysphasia	**2 (3%)**	**1 (1%)**	**0**	**0%**	**2**	**3%**	**6 (1 – 11)**
Paraesthesia	**2 (3%)**	**0**	**0**	**0%**	**2**	**3%**	**8 (1 – 16)**

	Within 8 weeks post infusion All Grades	Within 8 weeks ≥ Grade 3	>8 weeks to 1 year post infusion*		Anytime<1year All Grades No Grade 3 after 8 weeks		Duration of Events (start < 8wks) Median (Days) (Range)
Group Term	**N (%)**	**N (%)**	**N**	**%**	**N**	**%**	
Seizure	**2 (3%)**	**1 (1%)**	**0**	**0%**	**2**	**3%**	**2 (1 – 4)**
Depression	**1 (1%)**	**0**	**1**	**1%**	**2**	**3%**	**5 (3 -7)**
Mood Altered	**1 (1%)**	**0**	**1**	**1%**	**2**	**3%**	**121**
Amnesia	**1 (1%)**	**0**	**0**	**0%**	**1**	**1%**	**157**
Neuralgia	**1 (1%)**	**0**	**0**	**0%**	**1**	**1%**	**103**
Paresis	**1 (1%)**	**0**	**0**	**0%**	**1**	**1%**	**5**
Extrapyramidal Disorder	**0 (0%)**	**0**	**1**	**1%**	**1**	**1%**	**-**

Source: ADSL, ADAE, JMP; * No Grade 3 reported.

In general, neurologic events were concurrent with CRS but 8 (4 with headache alone) started before CRS, median time 1 day (range 1 – 4 days). Resolution of symptoms occurs over days to weeks and can lag behind CRS recovery (range of end of any neurotoxic event is 1 to 400 days). In addition, since one patient could have more than one event, there can be late events which were new events or recurrence of previous events such as insomnia. An example is a patient with an early CRS sleep disorder but encephalopathy does not develop until Day 29. New neurologic symptoms may also arise after the initial symptoms resolve. In eleven patients who had earlier neurologic events, new events occurred after CRS had resolved. Treatment for neurotoxicity has been symptomatic treatment which includes close monitoring and observation to assure the airway is maintained, seizure prophylaxis, and a symptomatic response that could involve corticosteroids. There was not a protocol recommended algorithm. There have been no reported cases of cerebral edema with tisagenlecleucel.

Reviewer Comment: The evaluation of neurologic adverse events is a complicated process. The applicant chose a screen of MedDRA terms based on non-infectious encephalitis. In doing so, the applicant eliminated headaches from their grouping. Headache as a symptom of disease may be non-specific. However, in a population which is younger, headaches may be more indicative of another medical complication. Therefore, it should be considered as part of the safety profile. Neurological toxicity, its components and symptomatic approach to therapy are part of the focus of the REMS ETASU. The neurologic toxicity has a strong component of encephalopathy with associated aphasia or dysphasia. In one patient, there was a prolonged incident of amnesia. While confusion requires little intervention other than reassurance, if patients become less responsive with their encephalopathy, the airway will need to be monitored to assure that there is no compromise. The REMS will take the symptomatic approach to neurologic complications similar to that used in the IND phase. The focus is the issue of encephalopathy with possible obtundation, seizures especially with prior history, and aphasia. While these events resolve over time, it will be important for patients, families, and healthcare providers to be aware that they may occur so that they can be medically managed with appropriate supportive care. The issue of neurotoxicity will also be discussed in the warnings and precaution section of the label.

Hemophagocytic Lymphohistiocytosis (HLH):
HLH is an inflammatory reaction that involves the activation of macrophages and T cells. It can be primary or secondary (sometimes associated with viral disease such as Epstein-Barr). In the context of CAR T-cell therapy, HLH has been seen in patients with increasing tumor load after the CAR T cells are administered. Five patients developed clinical HLH, 3 to 18 days after tisagenlecleucel (median 5 days). This correlates to the beginning of the expansion of tisagenlecleucel cells. HLH lasted a median of 5 days (range 2 to 20 days). Four were Grade 4 and one was Grade 3.

Reviewer comments: HLH and CRS have overlapping clinical symptoms. Of the 5 patients, all experienced CRS at Grade 3 or 4. HLH as a potential risk will be included in the label.

Febrile Neutropenia
There were 26 episodes of febrile neutropenia, predominately Grade 3 (n=24) as seen in Table 19 Adverse Events of Special Interest Post-tisagenlecleucel above.

Reviewer Comments: One of the major risks aside from CRS is the susceptibility of these R/R ALL patients to infections after tisagenlecleucel and for that matter while awaiting treatment as noted in Section 6.1.12.3. Due to both prior chemotherapy and LD, the patients were pancytopenic. This risk will need to be incorporated into the label.

Prolonged Cytopenias

Table 24: Hematology Parameter in the 8 weeks Post-Tisagenlecleucel

	Within 8 Weeks Post- Tisagenlecleucel (N=68) N (%)			
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (g/L)	**5 (7%)**	**31 (46%)**	**32 (47%)**	**0**
Leukocytes (10E9/L)	**0**	**2 (3)**	**6 (9)**	**60 (88)**
Lymphocytes (10E9/L)	**0**	**3 (4**	**19 (28)**	**43 (63)**
Neutrophils (10E9/L)	**0**	**1 (1)**	**5 (7)**	**59 (87)**
Platelets (10E9/L)	**12 (18)**	**6 (9)**	**10 (15)**	**37 (54)**

Source: ADLB

Table 25: Hematology Parameters 8 weeks to one year Post-Tisagenlecleucel

	8 weeks to 1 year post CTL019 infusion (N=68) N (%)			
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (g/L)	**20 (29)**	**14 (21)**	**4 (6)**	**0**
Leukocytes (10E9/L)	**13 (19)**	**17 (25)**	**12 (18)**	**8 (12)**
Lymphocytes (10E9/L)	**10 (15)**	**16 (24)**	**25 (37)**	**4 (6)**
Neutrophils (10E9/L)	**9 (13)**	**12 (18)**	**13 (19)**	**10 (15)**
Platelets (10E9/L)	**19 (28)**	**3 (4)**	**8 (12)**	**9 (13)**

Source: ADLB

Prolonged neutropenia and thrombocytopenia (after 30 days) has been noted after treatment with tisagenlecleucel. Twelve of the 52 responders to tisagenlecleucel had incomplete hematologic recovery by response definition over the 3 months for the evaluation. Twenty-five patients on B2202 experienced cytopenias after their infusion in the first 8 weeks. Blood count recovery was achieved by 6 months with improvements noted by 3 months.

Review Comment: The marrow recovery and immune dysfunction in these patients will need to be included in warnings and precautions on the label for the cited indication. As noted in the Tables above, while patient improved after 8 weeks, there were residual cytopenias recorded after 8 weeks. Risk of persistent neutropenia are infection and risk of persistent thrombocytopenia can increase the risk of bleeding. The label as well as the REMS with ETASU will insure the safe use of tisagenlecleucel. The focus of the ETASU is to train the sites, healthcare providers, patients, and families on the risk mitigation that is available.

Infections within 8 weeks after tisagenlecleucel administration

Forty patients on Study B2202 developed infections in the first 8 weeks after tisagenlecleucel administration. Seventeen infections were Grade 3, and two were Grade 4. The infections included gram-positive and gram-negative systemic infections, clostridium difficile, candida, herpes simplex, and human herpesvirus 6 in the central nervous system. One patient developed encephalitis consistent with Human Herpes Virus 6 (HHV6). This case was fatal on day 52. One other case of viral encephalitis was noted with HHV6 and CMV detected in cerebral spinal fluid. Another case of systemic HSV and HHV6 occurred which was concurrent with fungal sepsis.

Reviewer Comment: This population was pancytopenic for a minimum of 3-4 weeks awaiting response to tisagenlecleucel and return of marrow function once remission occurred. This infectious profile is expected in this highly pretreated population but it will need to be added to labeling to assure the safety of the patients treated with the commercial product. The rate of infection would be comparable to those that occurred.

Cardiac Disorders:

In the FDA review of the 68 patients in the safety set, 22 had cardiac events. There were multiple events in some patients. Grade 4 cardiac failure was noted in one patient, Grade 3 left ventricular failure (LVF) was noted in three patients and one of these patients with LVF also had right ventricular failure (Grade 1), mitral incompetence (Grade 1). Tachycardia Grades 1-4 also occurred in 18 patients within 8 weeks of the infusion.

Table 26: Cardiac Events in Safety Population

Cardiac Events	Patients N= 22	Median Duration (days)
Congestive Heart Failure[1]	**5**	**5 (range 4 to 205)**
Tachycardia[2]	**18**	**5.5 (range 1 to 25)**
Bradycardia[3]	**4**	**1.5 (range 1 to 3)**

[1]Left ventricular dysfunction, right ventricular dysfunction, cardiac failure, cardiac failure congestive, right ventricular dysfunction; [2]sinus tachycardia, tachycardia; [3]sinus bradycardia, bradycardia
Source: ADSL, ADAE

Reviewer Comment: Arrhythmias and congestive heart failure (CHF) are not commonplace in a pediatric population. This population was screened for arrhythmias and cardiac abnormalities ECHO and/or MUGA) as enrollment criteria and again evaluated pre-infusion with tisagenlecleucel. This population (R/R ALL) has a history of prior exposure to anthracyclines, other cardiotoxic chemotherapy, and prior HSCT which are considered in standard-of-care treatment for relapsed pediatric ALL which would predispose the patients to cardiac events, both CHF and arrhythmias. CHF can developed with severe CRS and improve with resolution of the CRS. The data for B2202 supports that the cardiac events generally did resolve. However, patients required therapy for their cardiac failure and for two patients this continued

after resolution of other tisagenlecleucel related toxicity. These two patients with cardiac events are on Enalapril for an arrhythmias (n=1) and CHF (n=1). The information regarding cardiac failure and arrhythmias will be included in the discussion of adverse events in the label due to the severity and seriousness of the events.

B-cell aplasia/Acquired hypogammaglobulinemia

As noted in the background section, tisagenlecleucel destroys normal B cells because they are CD19+. As a result, successful treatment resulted in acquired hypogammaglobulinemia. Patients have been maintained on supplemental treatment with intravenous gamma globulin (IV IgG) post- tisagenlecleucel. As long as the tisagenlecleucel cells persist, and so does the need for IV IgG. Hypogammaglobulinemia is reported in 24 of 68 patients in the safety set pre and post infusion of tisagenlecleucel. Pre-lymphodepletion, 2 patients are reported to have low IgG; during LD, only 1 patient, and post-tisagenlecleucel 24 patients. Post infusions 3 were Grade 3.

Reviewer Comment: This toxicity is on target but off tumor. It will need to be described in the label, including risk mitigation measures. Hypogammaglobulinemia is ameliorated with intravenous gamma globulin infusions. The tisagenlecleucel cells decrease normal B cells which produce gammaglobulin. However, the patients' previous chemotherapy could also have decreased their normal B cells and the incidence of hypogammaglobulinemia pre-tisagenlecleucel is consistent with the therapies that patients received for their ALL. There is no established data to indicate the ideal length of time that the tisagenlecleucel cells are needed to be active to assure clinical efficacy and they are known to persist in responders.

Bleeding Risk

Twenty seven patients experienced 61 episodes of bleeding. The cerebral hemorrhage occurred post-tisagenlecleucel and was fatal as detailed in Table 27. The Pre-treatment and lymphodepletion bleeding episodes reflect the chemotherapy that the patients were receiving. Post-tisagenlecleucel there was persistent cytopenias including thrombocytopenia (Table 27) and six patients had disseminated intravascular coagulation (DIC). Eight patients with CRS were noted to have fibrinogen less than the normal range. Bleeding was controlled with transfusion of fibrinogen, fresh frozen plasma and platelets.

Table 27: Bleeding Episodes Pre-treatment, Lymphodepletion, Post-tisagenlecleucel

		GR 1			GR 2		GR 3			GR 4	
Preferred Term	**Duration Median (Range) Days**	**Pre-tx**	**LD**	**Post-Tx**	**Pre-tx**	**Post-Tx**	**Pre-tx**	**LD**	**Post-Tx**	**Pre-tx**	**Post-Tx**
Anal Hemorrhage	1	0	0	1 (1%)	0	0	0	0	0	0	0
Catheter Site Hemorrhage	2	0	0	1 (1%)	0	0	0	0	0	0	0
Cerebral Hemorrhage	1	0	0	0	0	0	0	0	0	0	1(1%)
Conjunctival Hemorrhage	58.5 (1 - 118)	0	0	2 (3%)	0	0	0	0	0	0	0
Contusion	43 (7 - 47)	0	0	3 (4%)	0	0	0	0	0	0	0
Cystitis Hemorrhagic	25	0	0	0	0	1 (1%)	0	0	0	0	0
DIC	6.5 (3 -22)	0	0	0	0	4 (6%)	0	0	2 (3%)	0	0
Epistaxis	1 (2 - 12)	1 (1%)	1 (1%)	3 (4%)	0	2 (3%)	2 (3%)	1 (1%)	1 (1%)	0	0
Extradural	209	0	0	0	1 (1%)	0	0	0	0	0	0

Table 27: Bleeding Episodes Pre-treatment, Lymphodepletion, Post-tisagenlecleucel

		GR 1			GR 2		GR 3			GR 4	
Preferred Term	**Duration Median (Range) Days**	**Pre-tx**	**LD**	**Post-Tx**	**Pre-tx**	**Post-Tx**	**Pre-tx**	**LD**	**Post-Tx**	**Pre-tx**	**Post-Tx**
Hematoma											
GI Hemorrhage	1	0	0	0	0	1 (1%)	0	0	0	0	0
Gingival Bleeding	1 (1 -2)	0	2 (3%)	0	0	1 (1%)	0	0	0	0	0
Hemarthroses	13	0	0	0	0	0	0	0	1 (1%)	0	0
Hematemesis	1 (1 - 2)	1 (1%)	1 (1%)	1 (1%)	0	0	0	0	0	0	0
Hematoma	5	1 (1%)	0	0	0	0	0	0	0	0	0
Hematuria	6 (3 - 9)	1 (1%)	0	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0
Hemoptysis	1	0	0	0	0	1 (1%)	0	0	0	0	0
Hemothorax	45	0	0	0	0	0	0	0	0	1 (1%)	0
Melena	9	0	0	0	0	0	0	0	1 (1%)	0	0
Menorrhagia	32.5 (25 - 40)	0	0	1 (1%)	1 (1%)	1 (1%)	0	0	0	0	0
Mouth Hemorrhage	1 (1 - 12)	0	0	1 (1%)	1 (1%)	1 (1%)	0	0	2 (3%)	0	0
Petechiae	15 (1 - 36)	2 (3%)	1 (1%)	0	0	1 (1%)	0	0	1 (1%)	0	0
Pharyngeal Hemorrhage	5	0	0	0	0	1 (1%)	0	0	0	0	0
Purpura	2	0	0	1 (1%)	0	0	0	0	0	0	0
Tooth Pulp Hemorrhage	1	0	0	0	0	0	1(1%)	0	0	0	0
Vaginal Hemorrhage	27 (25 - 29)	0	0	1 (1%)	0	1 (1%)	0	0	0	0	0

Source: ADAERISK, JReview

Reviewer Comment: This is a medically challenging population. All of the patients on the trial had received multiple cycles of aggressive chemotherapy, up to about 2-3 weeks before lymphodepletion. CRS related coagulopathy is associated with clinical characteristics that include low fibrinogen. In addition, due to disease involvement in the bone marrow and chemotherapy, patients who received tisagenlecleucel were pancytopenic including thrombocytopenia. The complexity of the management of the patients justifies that the risk mitigation focus of the REMS ETASU that mimics the IND training program. This will need to be outlined in the label and included in the REMS with ETASU. With the label, the incidence of bleeding will need to be described to clarify the risks.

Secondary Malignancies

The median follow-up time for survival is 6.9 months (9 days to 17.7+ months). To date there have been no reports of secondary malignancies. There have been no reports of RCR generation and persistence of tisagenlecleucel has been observed up to 366 days thus far.

Reviewer comment: Although there are no safety events related to RCR generation and insertional mutagenesis, the risks of particularly for insertional mutagenesis are considered anticipated risks based on the mechanism of action and from safety data in the published literature for retroviral products. A post marketing required study is planned to further evaluate these risks. The possibility of B cell leukemia from transduction of B cell blasts or insertional

mutagenesis exists and may present as relapsed B cell leukemia, a number of factors were considered when making the recommendation to not recommend evaluation for insertional mutagenesis for B cell leukemia relapse. These included the a) present manufacturing specifications that minimizes the presence of B cell blasts in the product b) the planned manufacturing changes to further minimize the presence of B cell blasts in the product c) the sample sizes that may be required to assess the number of events based on the absence of a safety signal from Study B2202 d) the long-term monitoring studies that are ongoing under the IND e) the feasibility of obtaining additional samples in the post-marketing setting after the patient has been diagnosed with relapsed B cell leukemia. Evaluation of for insertional mutagenesis in patients with T-cell leukemia would be part of the monitoring for secondary malignancies.

Table 28: Treatment Algorithm for Infusion Reactions and CRS with tisagenlecleucel

CRS Treatment Algorithm
Pretreatment • Acetaminophen/paracetamol and diphenhydramine/H1 anti-histamine • Prophylaxis for complications of tumor lysis syndrome (TLS) as appropriate
Tisagenlecleucel infusion • Prodromal Syndrome: low-grade fevers, fatigue, anorexia (hours to days) • Observation, rule out infection (surveillance cultures) • Antibiotics per local guidelines (febrile neutropenia) • Symptomatic support
Symptom progression: High fevers, hypoxia, mild hypotension **1st Line Management:** • Oxygen, fluids, low dose vasopressor support, antipyretics • Monitor/manage complications of TLS
Further symptom progression • Hemodynamic instability despite intravenous fluids and moderate to "high dose" vasopressor support OR • Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow Oxygen (O2) and/or need for mechanical ventilation OR • Rapid clinical deterioration **2nd Line Management:** • Tocilizumab: IV infusion over 1 hour o Patient weight < 30 kg: 12 mg/kg IV o Patient weight ≥ 30 kg: 8 mg/kg IV (max dose 800 mg) • Hemodynamic and respiratory support
Lack of clinical improvement while awaiting tocilizumab response **3rd Line management** • Consider other diagnosis causing clinical deterioration (i.e., sepsis, adrenal insufficiency) • If no improvement with 1st dose of tocilizumab within 12 - 18 hours, consider steroids (plan rapid taper after hemodynamic normalization): o 2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day. As steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement. • If no response to steroids within 24 hours, consider 2nd dose of tocilizumab

(dosed as above) • Hemodynamic and respiratory support
Lack of clinical improvement while awaiting response to 3rd line management **4th Line Management** • Consider other diagnosis (e.g., sepsis, adrenal insufficiency) causing clinical deterioration • If no response to steroids and 2nd dose of tocilizumab within 24 hours or further clinical deterioration, consider siltuximab 11 mg/kg IV over 1 hour • Hemodynamic and respiratory support
Lack of clinical improvement while awaiting response to 4th line management **5th Line management** • Consider other diagnosis (e.g., sepsis, adrenal insufficiency) causing clinical deterioration • In ongoing CRS despite prior therapy, consider anti-T-cell therapies such as cyclophosphamide, anti-thymocyte globulin, or alemtuzumab • Hemodynamic and respiratory support

(Porter et al., 2015)

Reviewer Comment: Overall the safety profile for tisagenlecleucel has been manageable in the IND setting. The applicant had site training programs and close medical monitoring of adverse events to assure the safe use of tisagenlecleucel. After approval, this will need a REMS with ETASU to continue to the safe administration of the product and the safety of the patients receiving it.

In addition the applicant plans an observational PMR study B2410 to evaluate short and long term toxicity with tisagenlecleucel.

In order to continue to assure that the toxicity profile is manageable in the commercial setting, the label will need to have specific warnings and precautions to alert the clinicians not only to the risks of CRS and neurotoxicity and their management but to additional adverse events of special interest such as pancytopenia, infection risk, and bleeding.

6.1.12.6 Clinical Test Results

Table 29: Abnormal Blood Chemistries Within 8 Weeks Post-tisagenlecleucel

	Within 8 weeks post-tisagenlecleucel (N=68) N (%)			
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Alanine Aminotransferase (U/L)	**0**	**0**	**11 (16%)**	**2 (3%)**
Alkaline Phosphatase (U/L)	**1 (1%)**	**0**	**0**	**0**
Aspartate Aminotransferase (U/L)	**2 (3%)**	**3 (4%)**	**0**	**8 (12%)**
Bilirubin (umol/L)	**0**	**0**	**1 (1%)**	**0**
Creatinine (umol/L)	**11 (16%)**	**9 (13%)**	**4 (6%)**	**2 (3)**
Potassium (mmol/L)	**2 (3%)**	**1(1)**	**11 (16%)**	**9 (13%)**
Sodium (mmol/L)	**1 (1%)**	**1(1%)**	**10(15%)**	**20(29%)**
Magnesium	**0**	**1 (1%)**	**2 (3%)**	**0**

Source: ADSL ADLB

Table 30 Laboratory Investigations, Abnormal Blood Chemistries Post-tisagenlecleucel (8 weeks to 1 Year)

Table 30: Abnormal Blood Chemistries After 8 Weeks Post-tisagenlecleucel

	8 weeks to 1 year post–tisagenlecleucel (N=68) N (%)			
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Alanine Aminotransferase (U/L)	**4 (6%)**	**0**	**2 (3)**	**0**
Alkaline Phosphatase (U/L)	**3 (4%)**	**0**	**0**	**0**
Aspartate Aminotransferase (U/L)	**4 (6%)**	**3 (4%)**	**1 (1%)**	**0**
Bilirubin (umol/L)	**0**	**1 (1%)**	**1 (1%)**	**0**
Magnesium (mmol/L)	**0**	**0**	**2 (3%)**	**1 (1%)**
Potassium (mmol/L)	**3 (4%)**	**1 (1%)**	**1 (1%)**	**5 (7%)**
Sodium (mmol/L)	**0**	**1 (1%)**	**4 (6%)**	**8 (12%)**

Source: ADSL , ADLB. Table combines both abnormal elevations as well as lower than normal values.

Reviewer Comments: In general, these values reflect the clinical status of the patients on the trial.

6.1.12.7 Dropouts and/or Discontinuations

See Section 6.1.10.1.3 and Section 6.1.11.4.

6.1.13 Study Summary and Conclusions

See 7.1.11 and 8.6

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The proposed indication for tisagenlecleucel (KYMRIAH) is:

Tisagenlecleucel is a genetically modified autologous immunocellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL).

7.1.1 Methods of Integration

There was only one study B2202. See Section 6.

7.1.2 Demographics and Baseline Characteristics

See Sections 1.1 and 6.1.10.1.1.

7.1.3 Subject Disposition

See Section 6.1.10.1.3 and Section 6.1.11.4.

7.1.4 Analysis of Primary Endpoint(s)

See Section 6.1.9 for Methods and Section 6.1.11.1 for results.

7.1.5 Analysis of Secondary Endpoint(s)

See section 6.1.11.1 and 6.1.11.2 for results

7.1.6 Other Endpoints

None

7.1.7 Subpopulations

See Section 6.1.11.3

7.1.8 Persistence of Efficacy

See Section 6.1.11.2 for the analysis of duration of remission.

7.1.9 Product-Product Interactions

Tisagenlecleucel was used as a single agent.

7.1.10 Additional Efficacy Issues/Analyses

See Section 6.1.11.5

7.1.11 Efficacy Conclusions

In this BLA, the primary evidence of effectiveness comes from Study B2202. This single-arm, international, Phase 2 trial administered a single dose of tisagenlecleucel to pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia. The pre-specified primary endpoint for the licensure trial (CCTL019B2202), as defined by the applicant, was overall remission rate (ORR), as determined by the Independent Review Committee (IRC) assessment during the 3 months after tisagenlecleucel administration.

As of the November 23, 2016 cutoff, Study B2202 enrolled 88 patients, and 63 patients were infused with tisagenlecleucel manufactured in the U.S. facility. A total of 52 patients (82.5%) had a best overall disease response of CR or CRi, as determined by IRC. As a result, the lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is 70.9%, which is above the pre-set null hypothesis rate of 20%. Forty patients (63%) had a best response of CR within the first 3 months after infusion, and 12 patients (19%) had a best response of CRi. Among the 52 responders, the median DOR was not yet reached, with the median follow-up of 4.8 months.

These results of an overall remission rate of 82.5% with a median duration of response not yet reached in a heavily pre-treated population with relapsed/refractory pediatric and young adult acute lymphoblastic leukemia, even with a small sample size justifies a regular approval for tisagenlecleucel. These results with a single agent and no maintenance therapy indicate that the targeted tisagenlecleucel not only acutely treats the R/R ALL but has persistence that allows for a durable response unlike that seen with multiagent therapy or HSCT in a comparable historical population.

ORR was not considered an optimal endpoint for a regular approval regulatory decision-making for R/R B-cell precursor ALL. FDA has considered using durable CR for determination of clinical benefit on the basis of recovery of adequate blood counts to protect against infection and avoidance of transfusions. For the 63 patients in the efficacy analysis population, the CR rate

was 63% (95% CI, (50%, 75%), and all patients in CR were MRD negative. With a median follow-up of 4.8 months, the median duration of CR was not reached.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

See Section 6.1.12.1

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Tisagenlecleucel safety profile was demonstrated in a single trial B2202. The B2205J trial was also submitted for safety information but 26 of 29 patients received the UPenn CTL019 while 3 received tisagenlecleucel made in the MP facility. The CMC reviewers have determined that CTL019 products manufactured by UPenn and tisagenlecleucel manufactured by the Novartis Morris Plains Facility cannot be established based on the available comparability data in the BLA.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

See Section 1.1 and 6.1.10.1.1

8.2.3 Categorization of Adverse Events

See Section 6.1

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

There was no pooled data.

8.4 Safety Results

8.4.1 Deaths

See Section 6.1.12.3

8.4.2 Nonfatal Serious Adverse Events

See Section 6.1.12.4

8.4.3 Study Dropouts/Discontinuations

6.1.10.1.3 and Section 6.1.11.4.

8.4.4 Common Adverse Events

See Section 6.1.12.2

8.4.5 Clinical Test Results

See Section 6.1.12.6

8.4.6 Systemic Adverse Events

See Section 6.1.12.5

8.4.7 Local Reactogenicity

See Section 6.1.12.5; Infusion reactions.

8.4.8 Adverse Events of Special Interest

See Section 6.1.12.5

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

None

8.5.2 Time Dependency for Adverse Events

See Section 6.1.12.5

8.5.3 Product-Demographic Interactions

See Section 6.1.11.5

8.5.4 Product-Disease Interactions

Not applicable

8.5.5 Product-Product Interactions

None

8.5.6 Human Carcinogenicity

See Section 11.6

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable

8.5.8 Immunogenicity (Safety)

Per the clinical pharmacology review of anti-mCAR19 ab immunogenicity, the sponsor provided data on the cellular kinetics, and efficacy of tisagenlecleucel .

Anti-mCAR19 antibodies were measured in specimens collected pre- and post-tisagenlecleucel for the determination of humoral immunogenicity. Pre-infusion, anti-mCAR19 antibodies were observed in 90% of patients treated with tisagenlecleucel on B2202 . There is no apparent relationship between the $AUC_{0\text{-}28d}$ and presence of anti-mCAR19 antibodies at baseline indicating that pre-existing anti-mCAR19 antibodies did not impact the expansion and cellular kinetics of tisagenlecleucel.

Post-tisagenlecleucel, induced or boosted positive humoral immunogenicity was observed in 37% of patients treated with tisagenlecleucel on B2202.

Overall, there is no apparent relationship between pre-existing or treatment induced anti-mCAR19 antibodies on the cellular kinetics or impact on response or relapse.The data analysis is from Section 2.7.2 of the BLA.

8.5.9 Person-to-Person Transmission, Shedding

Not Applicable

8.6 Safety Conclusions

Severe CRS (Grade 3 and 4) events were noted in 49% of patients. These events are life-threatening and require supportive measures; 47% of all patients in the safety population required ICU admission, 53% of all treated patients required vasopressor or fluids to maintain blood pressure, 16% required mechanical ventilation, 12% required dialysis for a mean duration of 11 days (in the 8 weeks after tisagenlecleucel). Two fatal outcomes were related to severe CRS; one involved CRS related coagulopathy resulted in death of a patient from cerebral hemorrhage; and the second was the recurrence of leukemia and the onset of CRS that resulted in death 11 days after tisagenlecleucel. The CRS grading system and treatment algorithm are novel. For example, management of febrile neutropenia requires institution of IL-6 receptor blockade with tocilizumab and/or high dose steroid use. The treatment algorithm requires risk mitigation measures available (for example, availability of tocilizumab and siltuximab prior to tisagenlecleucel infusion) close monitoring to permit early intervention and extensive supportive care measures to manage the resultant multi-organ dysfunction and coagulopathy from CRS.

Transient but ≥ Grade 3 neurotoxicity such as encephalopathy, seizures, occurred in 18% of patients either during CRS or following resolution of CRS. Although transient, the severity of these toxicities requires monitoring for airway protection. The potential for anticipated fatal neurotoxicity exists, given the small sample size (n=68) of the safety population.

Severe infectious complications were noted in 26% (18/68) of patients, with three deaths occurring within 60 days and related to HHV6, bacterial pneumonia, and fungal infection. Management of these infectious complications are within the scope of the comprehensive risk management of patients with refractory and relapsed ALL.

Prolonged cytopenia (Grade 3+4) was noted in 37% of patients. Patients with prolonged neutropenia are at risk for infectious complications. However, these observations are expected complications in the intended population either secondary to the disease or related to available therapies. Since post-tisagenlecleucel, patients also experience acquired hypogammaglobulinemia due to the destruction of normal B cell, this increases the risk for infection.

Three patients experienced Grade 3 or 4 congestive heart failure requiring treatment for management. This safety event is an anticipated risk in the intended population with history of previous chemotherapy, prior HSCT and/or radiation therapy. However, one patient remains on therapy for the CHF.

As described in the CMC review, tisagenlecleucel is a genetically modified product that has the potential for integration of the lentiviral vector, clonal outgrowth, or neoplastic transformation of transduced host cells.

Overall, the issue of safety is crucial to the success of tisagenlecleucel for the treatment of R/R pediatric and young adult B-cell precursor ALL. To enhance safety, we will need to address the relevant issues using a three part approach. The product label will allow for a boxed warning as well as the warnings and precautions to convey a treatment algorithm for CRS. We have recommended a REMS with an ETASU to assure the safe use of tisagenlecleucel at participating sites for the commercial product not unlike the safeguards in place during the IND phase. Lastly, we have a postmarketing observational study that is a requirement. The applicant will follow for short and long term toxicity. In addition, to address the theoretical risk of insertional mutagenesis the sponsor will collect appropriate tissue samples through the PMR study. To date there have been no reports of secondary malignancies with tisagenlecleucel. There have been no reports of RCR generation. Persistence of tisagenlecleucel has been observed but follow-up is limited due to the short follow-up for the trial. The PMR study will attempt to obtain tissue from any second malignancy to determine if tisagenlecleucel is involved.

There is also the possibility of B-cell leukemia from transduction of B cell blasts. However, the applicant has manufacturing processes that include present manufacturing specifications that minimizes the presence of B cell blasts in the product and planned manufacturing changes to further minimize the presence of B-cell blasts in the product. Evaluation of for insertional mutagenesis in patients with T-cell leukemia would be part of the monitoring for secondary malignancies.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data with tisagenlecleucel use in pregnant women to determine whether there is product-associated risk. It is unknown if tisagenlecleucel can cause fetal harm when administered to a pregnant woman or can affect fertility. If tisagenlecleucel crosses the placenta, it may cause fetal toxicity including B-cell lymphocytopenia. Therefore tisagenlecleucel is not recommended for women who are pregnant.

Pregnancy status of females with reproductive potential should be verified. Females of reproductive potential should have a pregnancy test prior to starting treatment with tisagenlecleucel.

In addition, for patients who receive lymphodepleting chemotherapy, fludarabine and cyclophosphamide, will also need effective contraception. This includes males and females. Pregnancy in the patients or their partner should be discussed with the tisagenlecleucel treating physician.

Infertility

There are no data on the effect of tisagenlecleucel on fertility.

9.1.2 Use During Lactation

There is no information regarding the presence of tisagenlecleucel in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tisagenlecleucel and any potential adverse effects on the breastfed infant from tisagenlecleucel or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

This study B2202 was conducted in a pediatric population ages: 2 to < 12 (50%); 12 to < 17 (25%) in the enrolled set. Similar percentages were noted in the safety and efficacy sets. No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial. The applicant submitted a request for FDA to issue a written request (WR) for B2202 and this was done in December 1, 2016. The applicant completed the WR prior to the submission of the BLA and it was reviewed by the PeRC and the CBER Pediatric Exclusivity Board. The applicant met their endpoints for the WR.

9.1.4 Immunocompromised Patients

Due to the nature of the chemotherapy that patients with R/R B-cell precursor ALL receive, they are all immunocompromised at the time that they receive tisagenlecleucel.

9.1.5 Geriatric Use

The safety and effectiveness of tisagenlecleucel in combination with lymphodepleting chemotherapy have not been established in geriatric patients. Clinical studies of tisagenlecleucel for this indication did not include patients age 65 years and over.

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

None

10. CONCLUSIONS

In this BLA, the primary evidence of effectiveness comes from Study B2202. This single-arm, international, Phase 2 trial administered a single dose of tisagenlecleucel to pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia. The pre-specified primary endpoint for the licensure trial (CCTL019B2202), as defined by the applicant, was overall remission rate (ORR), as determined by the Independent Review Committee (IRC) assessment during the 3 months after tisagenlecleucel administration.

As of the November 23, 2016 cutoff, Study B2202 enrolled 88 patients, and 63 patients were infused with tisagenlecleucel manufactured in the U.S. facility. A total of 52 patients (82.5%) had a best overall disease response of CR or CRi or 49 patients achieved CR/CRh (78%) as determined by IRC and FDA respectively. As a result, using the pre-specified endpoint in the SPA for B2202, the lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is 70.9% for CR/CRi, which is above the pre-set null hypothesis rate of 20%. Forty patients (63%) had a best response of CR within the first 3 months after infusion, and 12 patients (19%) had a best response of CRi. Among the 52 responders, the median DOR was not yet reached, with the median follow-up of 4.8 months.

ORR was not considered an optimal endpoint for a regular approval regulatory decision-making for R/R B-cell precursor ALL. FDA has considered using durable CR for determination of clinical benefit on the basis of recovery of adequate blood counts to protect against infection and avoidance of transfusions. For the 63 patients in the efficacy analysis population, the CR rate was 63% (95% CI, (50%, 75%), and all patients in CR were MRD negative. With a median follow-up of 4.8 months, the median duration of CR was not reached.

Overall, the issue of safety is crucial to the success of tisagenlecleucel for the treatment of R/R pediatric and young adult B-cell precursor ALL. To enhance safety, FDA concludes that there should be a comprehensive plan to insure safety after licensure. First, the product label should address with warnings and precautions for the key safety issues identified in B2202, and convey a treatment grading system and algorithm for CRS. There will be a REMS with an ETASU to assure the safe use of tisagenlecleucel at participating sites for the commercial product not unlike the safeguards in place during the IND phase. Lastly, there will be a postmarketing observational study that is a requirement to follow recipients of the commercial product for short and long term toxicity. If a second malignancy, the applicant will attempt to obtain tissue to test for involvement by the tisagenlecleucel.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Benefit Considerations

- Tisagenlecleucel was given as a single infusion after lymphodepleting chemotherapy to 63 pediatric and young adult patients with R/R B-cell precursor ALL. The ORR was 82.5% with 52 patients with a best overall response of CR (n=40 [63%]) or CRi (n=12) as determined both locally and by an IRC.
- All of the responders were MRD negative
- The responses were durable. 29 of 52 patients were still in remission as of the data cut-off of November 23, 2016. The median follow-up time for DOR was 4.8 months (Range: 1.2 – 14.1 months). The median DOR was not reached.
- Overall survival: 11 patients (17.5%) died after tisagenlecleucel infusion. Seven patients received HSCT in remission after receiving tisagenlecleucel. Fourteen patients went on to other chemotherapy without HSCT. No deaths occurred from CRS. The median follow-up time for OS was 6.9 months (min=9 days, max=17.7 months). Median OS was 16.7 months (95% CI: 16.7, NE).

Risk Considerations

- Severe CRS (Grade 3 and 4) events were noted in 49% of patients. These events are life-threatening and require supportive measures such as 46% of all patients required ICU admission.
- One fatal outcome from severe CRS related coagulopathy resulted in death of a patient from cerebral hemorrhage.

- Transient but ≥ Grade 3 neurotoxicity such as encephalopathy, seizures, occurred in 18% of patients either during CRS or following resolution of CRS
- Severe infectious complications were noted in 26% (18/68) of patients, with three deaths occurring within 60 days and related to HHV6, bacterial pneumonia, and fungal infection. Management of these infectious complications are within the scope of the comprehensive risk management of patients with refractory and relapsed ALL.
- Prolonged cytopenia was noted in 37% of patients. Patients with prolonged neutropenia are at risk for infectious complications. 59% of patients experienced infections post-tisagenlecleucel.
- Three patients experienced Grade 3 or 4 congestive heart failure requiring treatment for management.
- As described in the CMC section, tisagenlecleucel is a genetically modified product that has the potential for integration of the lentiviral vector, clonal outgrowth, or neoplastic transformation of transduced host cells
- Prolonged hypogammaglobulinemia due to on target, off tumor destruction of normal B cells, which necessitates the use of routine infusions of intravenous gammaglobulin.

Available therapies for R/R pediatric and young adult patients with R/R B-cell precursor ALL

- Combination therapies of known chemotherapeutic agents used with initial diagnosis and prior treatment of relapse.
- If a CR can be obtained, a HSCT, which has improved results if done when the patient is MRD negative.
- Single agent approved therapies for pediatric and young adults: Similar approved agents given alone had an ORR of 33% (blinatumomab), 20% (clofarabine), and 10% (Vincristine sulfate liposome injection) which is only approved for adults. Duration of remission for all three ranged from 2 to 6 months.

Table 31: Benefit Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ALL is the most common childhood malignancy with 3100 cases per year with a 90% 5 year overall survival rate • Patients with primary refractory disease are rare. Disease-free survival at 5 years for MRD+ at end of consolidation is 39% • Incidence of relapsed or refractory (R/R) disease is 20% at any site. • Response to treatment for relapsed disease is dependent on the time from original diagnosis and site of the relapse • Five-year disease-free survival (DFS) for CR2 and CR3 were 27% and 15%.	• ALL after second or subsequent relapse or refractory to initial induction chemotherapy is highly resistant to salvage chemotherapy based on prior exposure to standard of care chemotherapy and stem cell transplantation • R/R ALL is a serious condition based on the poor prognosis with standard of care therapy which includes HSCT

Unmet Medical Need	• There is a potential incidence of 600 refractory/relapsed patients per year which would include isolated extramedullary disease and initial relapse. • Standard of care therapies for second or subsequent systemic relapses do not produce sustained remissions • In the absence of a MRD-negative complete response, the benefit of HSCT is limited	• In children and young adults age 3-23 with primary refractory disease or second or subsequent relapse, there is an unmet medical need for additional therapies.
Clinical Benefit	• B2202 was a single-arm, multisite, international study for the treatment of pediatric and young adult patients with relapsed or refractory ALL with tisagenlecleucel • The patients were treated with one course of lymphodepleting chemo-therapy followed by a single infusion of tisagenlecleucel. • The primary endpoint was ORR (CR+CRi), and the objective was to demonstrate an ORR that excluded 20%. • In the Efficacy Analysis Set (n-63), the ORR was 82.5% (95% CI 70.9, 91.0). The CR rate was 63.4% (95% CI 50.4, 75.3) • With a median follow-up of 4.8 months, the median duration of remission was not reached. • All remissions were MRD-negative.	• The evidence for clinical benefit for R/R ALL in pediatric and young adults is compelling.
Risk	• The most substantial risks of tisagenlecleucel were cytokine release syndrome (CRS), neuropsychiatric events, prolonged cytopenias, infectious complications, cardiac events, persistence of hypogammaglobulinemia.	• All the evidence indicates that the risk of tisagenlecleucel, while substantial, does not outweigh the benefit to R/R ALL in pediatric and young adults as defined in the B2202 study.
Risk Management	• The most substantial risks of tisagenlecleucel are associated with CRS and neurologic toxicity events. These were mitigated in the trial by careful site selection and training of investigators. • There are theoretical risks for second malignancy in this genetically modified immunotherapy based on the potential for replication competent retrovirus due to the lentivirus and insertional mutagenesis.	• The risks associated with tisagenlecleucel warrant boxed warnings, a REMS with ETASU and a long-term follow-up study. • B2410 is a postmarketing study to follow 1000 recipients of the commercial product for 15 years for second malignancy and other safety signals. • The OBE reviewers are working with the applicant to establish a REMS with elements to assure safe use.

11.2 Risk-Benefit Summary and Assessment

The risks of tisagenlecleucel center are related to its mechanism of action, which is activation of T cells and the destruction of CD19+ B cells, including normal B cells. Cytokine release syndrome, which occurred 79% of the patients, can be life-threatening or fatal. Hypogammaglobulinemia persists for months and requires monitoring and intervention. Nonetheless, the CR rate of 63% is substantial for this population that has failed multiple standard therapies. Overall the benefit/risk profile for these heavily-pretreated pediatric and young adult patients with R/R B-cell precursor ALL is favorable with appropriate risk mitigation strategies in place.

11.3 Discussion of Regulatory Options

The review team weighed accelerated approval and regular approval for this product. The CR rate in a single-arm trial is frequently used as a surrogate reasonably likely to predict clinical benefit for accelerated approval of new drugs for acute leukemia, but a durable CR rate of

remarkably high magnitude might also be considered a direct clinical benefit in a population that has failed multiple therapies and has no reasonable alternative treatments. The latter would apply to the CR rate and study population in B2202, making regular approval a reasonable recommendation. The consideration was complicated by the study design which a) did not require restaging prior to start of study treatment, and b) required use of two active chemotherapeutics in the study regimen in addition to tisagenlecleucel. Under such circumstances, in order to isolate demonstrate the effect of a new biologic in isolation, a randomized trial is generally expected, but the magnitude of the CR rate in B2202 was far greater than would be anticipated with any chemotherapy, raising questions about whether there would be sufficient equipoise to pursue a randomized trial. The review team therefore concluded that based on the results of B2202, regular approval of tisagenlecleucel was appropriate for the intended population of pediatric and young adult patients up to age 25 with relapsed (second or greater relapse) or refractory (primary resistant to two induction regimens) B-cell precursor ALL. The age was lowered due the known incidence of pediatric ALL in children younger than 3. Apheresis is possible in most children who are over 10 kilograms in weight and younger patients who relapse in this age group would benefit from the product.

However, the safety profile for tisagenlecleucel as documented in this review warrants a REMS with ETASU prior to a clinical site giving tisagenlecleucel. 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 not only treated appropriately but that patients and medical staff were educated on the risk particularly of CRS. There are additional long-term safety concerns due to the use of the lentiviral vector. As discussed in the Oncologic Drugs Advisory Committee, with the CBER Safety Working Group, and with our colleagues in the Office of Biostatistics and Epidemiology, we are asking the applicant to comply with a PMR study for short and long-term toxicity with an observational focus. However, in the event of a second malignancy the applicant will attempt to secure tissue to ascertain if tisagenlecleucel was involved in the malignant process. Lastly, the label will need to be inclusive of the risks and include risk mitigation strategies for CRS and neurotoxicity.

11.4 Recommendations on Regulatory Actions

The review team recommends regular approval (21 CFR 601.4) for tisagenlecleucel (Kymriah).

11.5 Labeling Review and Recommendations

The revised package insert (PI) was reviewed, comments, and/or revised by the appropriate discipline reviewers. APLB conducted its review from a promotional and comprehension perspective. Labeling meetings with the applicant are ongoing at the time of completion of this review.

11.6 Recommendations on Postmarketing Actions

The applicant submitted a postmarketing study which we will consider a postmarketing requirement. This study B2401 is observational and focuses on short-term toxicity, documenting adverse events, OS and long-term follow-up for documentation and evaluation of second malignancies. No routine study for RCR or persistence is planned. The applicant plans as part of B2401 to make every effort to obtain tissue from second malignancy to assure that tisagenlecleucel has not caused the second malignancy or insertional mutagenesis. The plan is to enroll 1000 patients over 5 years and follow each patient for 15 years.

The applicant submitted a risk evaluation mitigation strategy (REMS) that consisted of a communication plan and medication guide. We determined in consultation with the OBE and CDER DRISK that a REMS with elements to assure safe use (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 (FDA Draft Guidance, September 2016).

The REMS ETASU should be reviewed, approved, and implemented by the applicant at participating treatment sites for tisagenlecleucel prior to the distribution of tisagenlecleucel to the site. Please see Section 4.6 for specific details of the REMS ETASU.

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Appendices

Table 32 Appendix A: University of Pennsylvania Cytokine Release Syndrome Grading System

The Penn Grading Scale for CRS			
1	**2**	**3**	**4**
Mild reaction: Treated with supportive care such as anti-pyretics and anti-emetics	Moderate reaction: Requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e., grade 2 creatinine or grade 3 liver function tests [LFTs] related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids* or low-dose pressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, continuous positive airway pressure [CPAP] or bilateral positive airway pressure {BiPAP]. Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS	Life-threatening complications such as hypotension requiring high-dose pressors or hypoxia requiring mechanical ventilation

- Marked elevations in IL-6, interferon gamma, and tumor necrosis factor (TNF)
- Symptoms occur 1-14 days after cell infusion in ALL
- Symptoms may include: High fevers, rigors, myalgia, arthralgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea, and hypoxia
- The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (e.g., sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours.

*Defined as multiple fluid boluses for blood pressure support

High-Dose Vasopressor Recommendations

Definition of "High-Dose" Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine monotherapy	≥ 0.1 mcg/kg/min
If on vasopressin	High-dose if vaso + Norepinephrine (NE) of ≥ 0.1 mcg/kg/min (using VASST formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min (using VASST formula)
VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) + 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) +10] Criteria from Russell et al 2008 Note: Pediatric weight adjustment should be taken into consideration.	

Source: Porter, 2015

Table 33 Appendix B: Safety and Efficacy Monitoring

Phase	SCREENING	Pre-Treatment			Treatment and Primary Follow-up (F/U)															Survival F/U
Visit Name	W-16 to W-12	ENROLLMENT/Pre LD	LD/CHEMO	PRE-INFUSION	INFUSION	Post-Infusion														
Study Day (D) Week (W)		W-16 To D-12	D-14 To D-2	D-1+1	D1	2	4	7	11	14	17	21	28	M2, 3, 4, 5, 6	M9, 12	M 15, 18, 21	M 24, 36, 48	M 30, 42, 54	M60	Q 3 m
Patient History	X																			
Hospitalization		From Screening to Month 2																		
Lymphodepleting Chemotherapy			X																	
Bridging chemotherapy	As clinically needed																			
Pre-CTL019 Assessment					X															
CTL019					X															
Chemo-Post							X	X	X	X	X	X	X	X	X	X	X	X	X	
Labs																				
Hematology	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CRP, fibrinogen, ferritin,	X				X	X	X	X	X	X	X	X	X							
Coags	X		X		X			X		X			X							
Influenza A and B					X															
Serum immunoglobulin levels	X									X			X	X	X					
MUGA / ECHO	X																			
Disease Assessments																				
Bone Marrow	X												X	Not CR/CRi on D28, need assessment at time of response; M 3, 6 recommended only						
BM MRD, flow, qPCR	X												X	Not CR/CRi on D28, need assessment at time of response; M 3, 6 recommended only						

Tumor by flow in PB	**X**							**X**		**X**		**X**	**X**	**X M3 & 6**	**X**	**X M 18 only**	**X**	**X**	**X**	
CSF	**X**												**X**	**Required at first Assessment of CR/CRi**						
MRI	**As clinically indicated**																			
Extra-medullary Disease	**X**												**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Relapse														**Assess for relapse every 3 months, first new therapy for relapse should be recorded**						
Safety																				
AEs, new malignancies, significant findings														**Report when they occur. Survival F/U every 3 months**						
Immunogenicity serum		**X**								**X**			**X**	**X M3, 6**	**X M12**	**If relapses, collect sample**				
Immunogenicity Peripheral blood		**X**								**X**			**X**	**X M3, 6**	**X M12**	**If relapses, collect sample**				
RCR by VSV-G 1PCR		**X**												**X M3, 6**	**X M12**		**X**		**X**	
Transgene Persistence (PB)														**M 3,6**	**M9, 12**	**M 24**	**M 36**	**M 48**	**M 60**	
Biomarkers																				
Cytokines		**X**			**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X M3, 6**	**X M12**					
CRS assessments Anticytokine therapy PK CTL019 PK, cytokines and IL-6R, inflame., markers					**As clinically indicated**															
CTL019 PK by flow - PB		**X**			**X**		**X**	**X**	**X**	**X**		**X**	**X**	**M3, 6**	**X**	**X M 18**	**X**	**X**	**X**	
CTL019 PK and nl T cells by qPCR - PB	**X**												**X**	**Recommended with first CR, CRi response**						
CTL019 PK by qPCR in BM, flow in BM qPCR in CSF	**X**												**X**	**Recommended with first CR, CRi response**						
CTL019 Immunophenotyping by flow PB		**X**						**X**		**X**		**X**	**X**	**M3, 6**	**X**		**X M 24, 36**			
End of Phase Disposition		**X**		**X**															**X**	

Source: Adapted from B2202 Protocol in Appendix 16 of Legacy Study Report in Section 5.3.5.2 of the BLA

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This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

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