FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

BLA 125646
Tisagenlecleucel
Novartis Pharmaceuticals Corporation

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the BLA for tisagenlecleucel, a first-in-class product, with the applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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ABBREVIATIONS
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
CHF	CONGESTIVE HEART FAILURE
CI	CONFIDENCE INTERVAL
CMV	CYTOMEGALOVIRUS
CNS	CENTRAL NERVOUS SYSTEM
CR	COMPLETE REMISSION
CRH	COMPLETE REMISSION WITH HEMATOLOGIC RECOVERY
CRI	COMPLETE REMEISSION WITH INCOMPLETE HEMATOLOGIC RECOVERY
CSF	CEREBROSPINAL FLUID
CT	COMPUTED TOMOGRAPHY
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
D	DAY
SDOR	DURATION OF RESPONSE
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
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
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
SCFV	SINGLE-CHAIN VARIABLE FRAGMENT
SD	STABLE DISEASE
SIN	SELF-INACTIVATING

SPA	SPECIAL PROTOCOL ASSESSMENT
TCR	T CELL RECEPTOR
TKI	TYROSINE KINASE INHIBITOR
US	UNITED STATES
VCN	VECTOR COPY NUMBER
WAS	WISKOTT-ALDRICH SYNDROME

1. PROPOSED INDICATION

The proposed indication for tisagenlecleucel is 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).

2. EXECUTIVE SUMMARY

Topic

The Oncologic Drugs Advisory Committee (ODAC) is being convened to discuss the applicant's biologics license application for tisagenlecleucel, 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).

Tisagenlecleucel is comprised of genetically-modified antigen-specific autologous T cells that have been reprogrammed to target cells that express CD19. CD19 is an antigen expressed on the surface of 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.

Issues

The primary evidence of effectiveness is based on Study CCTL019B2202 (B2202) a Phase 2 study. The primary endpoint was overall remission rate (ORR), defined as a best overall response rate (BOR) of complete remission (CR) or complete remission with incomplete blood count recovery (CRi) as determined by Independent Review Committee (IRC) assessed during the 3 months after tisagenlecleucel administration with the initial assessment occurring on Day 28. Bone marrow exams were performed 4 weeks after the initial assessment or at the time of first CR to assess for minimal residual disease (MRD), a predictor of long-term remission. The study would meet its primary objective if the lower bound of the 2-sided 95% exact Clopper Pearson confidence intervals (CI) for ORR was greater than 20%. Bone marrow exams were performed 4 weeks after the initial assessment or at the time of first CR to assess for minimal residual disease (MRD), a predictor of long-term remission.

The primary efficacy analysis was based on 63 subjects who received a single intravenous infusion of tisagenlecleucel that was manufactured at US facility site, and resulted in an ORR of 82.5% (52/63) with the 95% CI (70.9, 91.0) in treated subjects.

In addition, all of the CRs or CRi's were associated with MRD-negative status in the bone marrow (BM). The overall effectiveness of this product is not the primary issue for consideration by this Committee.

In Study B2202, the safety analysis population consisted of 68 subjects. The serious adverse events observed in this study included life-threatening cytokine release syndrome (CRS) and hemophagocytic lymphohistiocytosis (HLH), neurological events that occurred with CRS or delayed after the resolution of the CRS, coagulopathies with CRS, and life-threatening infections. Grades 3 or 4 CRS occurred in 32 subjects (47%) of the subjects. There were no deaths from CRS. Neurological toxicities included encephalopathy, delirium, hallucinations, somnolence, cognitive disorder, seizure, depressed level of consciousness, mental status changes, dysphagia, mental status changes, muscular weakness, and dysarthria in 30 (44%) subjects treated with tisagenlecleucel.

In addition to the short-term safety issues noted above, potential long-term safety concerns with tisagenlecleucel include the potential for generation of replication-competent retrovirus (RCR) and the potential for insertional mutagenesis to cause new malignancies (genotoxicity). The safety assessments in Study B2202 did not identify risks from clonal outgrowth and vector-mediated delayed adverse events (e.g., secondary leukemias). However, most study subjects have not been followed for very long, thus limiting the ability to assess the risk of delayed events. The potential for genotoxicity from insertional mutagenesis is a concern with immunotherapy products that require gammaretroviral and lentiviral transduction. Therefore, post-marketing considerations for long-term safety monitoring may be necessary to address the potential safety concern.

The FDA seeks the opinion of the Committee regarding 1) post-marketing considerations for risk mitigation for short-term toxicities, particularly cytokine release syndrome, and 2) long-term follow-up for anticipated safety concerns related to the potential for insertional mutagenesis and secondary malignancies 3) whether the benefits justify the risks for a marketing approval of tisagenlecleucel for the proposed indication.

The Committee discussion of the manufacturing aspects that influence long-term follow-up is scheduled to occur in the morning session, with additional discussion of long-term follow-up and short-term risks scheduled to occur in the afternoon session.

Please refer to Section 10 of this document for our draft points for the committee to consider.

3. BACKGROUND

Pediatric and Young Adult Acute Lymphoblastic Leukemia (ALL) Overview

The incidence of new cases of pediatric ALL is approximately 3100 in children and adolescents per year (PDQ, HCP April 2017). Although ALL can be of either T or B cell origin, approximately 80-85% are of B cell origin. Current treatment for *de novo* or relapsed B cell in

pediatric ALL, and young adult ALL, includes combinations of chemotherapy, radiation therapy, and HSCT and is risk-based.

The survival after relapse depends on the timing of the relapse and the type of the relapse. Relapses that occur within 18 months of initiation of therapy or while the patient is still on therapy have an extremely poor prognosis despite subsequent therapy. Extramedullary relapse alone without systemic relapse may be salvageable with systemic therapy as well as therapy directed specifically to the site of relapse. With more aggressive therapies for front-line treatment, salvage therapy has become less effective. The only potential cure for relapse in recurrent pediatric ALL has been allogeneic stem cell transplantation (HSCT). Unfortunately, for the HSCT to succeed, the patient needs to be in CR, preferably MRD negative (< 10e-2) (Pulsipher et al., 2014).

In addition to hematopoietic stem cell transplantation (HSCT), the agents described in Table 2 below have been approved for the treatment of r/r ALL. BLINCYTO and CLOLAR are FDA-approved for treatment of relapsed or refractory pediatric ALL. However, the standard of care for relapsed/refractory ALL in pediatric and young adult patients is investigator choice, which usually includes a combination therapy with intent to proceed to HSCT if an appropriate donor is identified. Since the disease remains responsive to repeat first-line therapy in about half of this population, the first-line use of combination therapy is reasonable, even though the responses are of short duration and this remission interval decreases with each combination treatment given. The short duration of response and decreased remission interval with available combination therapies underscores the importance of an analysis of the duration of response in subjects treated with tisagenlecleucel. If responses were of short duration, then the benefits might not justify the risks. The annotated approval information for these alternative therapies listed in Table 1.

Table 1. FDA-Approved Therapies for r/r ALL

FDA-Approved Products	Approval Year	Endpoint(s)	Clinical Benefit / Effect
BLINCYTO	2014	ORR = CR +CRh	N=70; median age 8 (7 months-17 years; 57% prior transplant; median treatment 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)
MARQIBO	2012	ORR= CR + CRi	Approval in Ph chromosome-negative adult r/r ALL N=65; relapsed or refractory after 2 or more therapies; 48% prior transplant; 45% under 30. CR 3 (4.6%); CRi 7 (10.8%); CR+CRi

FDA-Approved Products	Approval Year	Endpoint(s)	Clinical Benefit / Effect
			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)
CLOLAR	2004	ORR=CR +CRp	N=61 r/r ALL. r/r to 2 or more prior therapies. CR% 11.5% (4.7, 22.2; CRp%: 8.2%; PR; DOR: 10.7 weeks (2.5 months) censored at transplant

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})
r/r: relapsed/refractory
Source: PI for BLINCYTO, MARQIBO, CLOLAR

Minimal Residual Disease (MRD) in pediatric ALL

Allogeneic HSCT is recommended in pre-B cell pediatric ALL with very high-risk disease such as induction failure and/or poor cytogenetic profile; second CR after early BM relapse (< 36 months), and any patient in third CR. MRD noted before HSCT predicts relapse after transplant (Pulsipher et al., 2014).

Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a systemic response to the activation and proliferation of CAR T cells, in this case tisagenlecleucel. CRS includes a spectrum of clinical events, including (but not limited to) high fevers, hypoxia, hypotension, malaise. Frey and Porter (2016) published a recent review of anti-CD19 Chimeric Antigen Receptor (CAR) T cell therapy. They described CRS, neurotoxicity, and other complications. CRS generally occurs within 1 to 14 days after anti-CD19 CAR T cell therapy. Duration is variable depending on severity and interventions needed. CRS is associated with elevated cytokines including interferon-γ, IL-2 receptor α, IL-6, and IL-10. CRS and hemophagocytic lymphohistiocytosis (HLH) (macrophage activating syndrome) have many similarities. Therapy is symptomatic and there has been some reported success with anti-interleukin 6 (IL-6) therapy and/or corticosteroids. Treatment of CRS during Study B2202 was symptomatic, along with use of an anti-IL6 receptor blocker, tocilizumab, in the event of Grade 3 or Grade 4 CRS. Early in the clinical development of engineered T cells, it was noted that IL6 was elevated in CRS and that CRS might respond to tocilizumab. Subjects with Grade 3 or 4 CRS, as noted below, often require intensive care that may include vasopressor and ventilatory support. The prompt recognition of the symptoms of CRS, and administration of tocilizumab, may contribute to successful management of CRS. Follow-up data related to the management of CRS with tocilizumab is short (< 5 years).

CRS has known risk factors. Subjects with ALL have a higher incidence of CRS with anti-CD19 CAR products. Patients with bulky disease (> 50% BM involvement at the time of screening for tisagenlecleucel administration) have an increased risk of CRS. Higher doses of transduced cells may also increase the risk of CRS (Porter et al., 2015).

The clinical symptoms of CRS are associated with increased inflammatory markers (C-reactive protein [CRP], ferritin, interferon-γ, and interleukin-6 (IL-6). Additional cytokines are also elevated; soluble interleukin-2 receptor α, and cytokines (e.g., IL-6 and IL-10) associated with macrophage activation. CRS is similar in its clinical profile to macrophage activating syndrome/hemophagocytic lymphohistiocytosis.

Neurotoxicity is generally reversible. It often occurs with CRS but may occur while the patient is recovering from CRS or without CRS. Anti-CD19 CAR T cells can cross into the cerebral spinal fluid (Hu et al., 2016). Cerebral edema has been reported with CD19-directed CAR T cell therapy (Hu et al., 2016).

Table 2. Regulatory Milestones

Date	Milestone
4/22/2013	PreIND Meeting
3/03/2014	PreIND Meeting
3/04/2014	Special Protocol Assessment (SPA)
9/23/2014	IND 16130 submission
9/23/2014	Rare Disease Designation
1/31/2014	Orphan Designation: Acute Lymphoblastic Leukemia
4/08/2015	First subject enrolled into Study CCTL019B2202
2/29/2016	Breakthrough Therapy Designation
11/21/2016	Pre-BLA Meeting
11/23/2016	Efficacy Assessment: Data Cut-off
12/16/2016	CCTL019B2202 Interim Analysis with 6 months follow-up
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
7/12/2017	Oncologic Drugs Advisory Committee Meeting
10/03/2017	PDUFA Action Due Date

4. CHEMISTRY, MANUFACTURING, AND CONTROLS

This section provides background information pertaining to the manufacturing and control of tisagenlecleucel, but does not disclose any proprietary information. This section focuses on product characteristics and critical quality attributes related to safety and biological activity. Also discussed are possible risks associated with retroviral[1] vector-based gene therapy products, including the potential for generation of replication-competent retroviruses (RCR)[2] and vector-induced genotoxicity. Strategies that the applicant is using to mitigate these risks, such as comprehensive RCR testing of the retroviral vector and tisagenlecleucel, and patient monitoring for delayed adverse events related to insertional mutagenesis are outlined. Discussion questions for the Committee relate specifically to tisagenlecleucel, but the FDA invites discussion that would apply more generally to the class of CAR T cell products.

4.1 Discussion Point 1: Manufacturing process controls and product quality attributes contributing to safety and activity

4.1.1 Control of tisagenlecleucel quality through manufacturing process controls

A major consideration for manufacturing tisagenlecleucel is the establishment of a well-controlled manufacturing process that can consistently produce high-quality CAR T cells that are safe, pure, and potent. Consistency in product quality is necessary to provide reasonable confidence that each lot (batch) of tisagenlecleucel will perform as expected at a given dose in patients.

In order to control the manufacturing process for consistency, it is necessary to thoroughly understand the manufacturing process and critical product quality attributes unique to the autologous CAR T cell products. It is also critical to understand and address sources of variability seen in the individual products. This can be a challenging issue given the complex and labor-intensive manufacturing processes involved with making a CAR T cell product (Figure 1). These challenges can include variability in the starting materials (e.g., patient's own leukapheresis cells) and human or animal derived reagents (e.g., serum, antibodies); and control of critical components that may be manufactured under contract (e.g., transfer vectors that encode CAR, final container).

[1] Lentiviral vectors are a form of retroviral vector.
[2] Replication competent lentivirus (RCL) is a form of replication competent retrovirus (RCR)

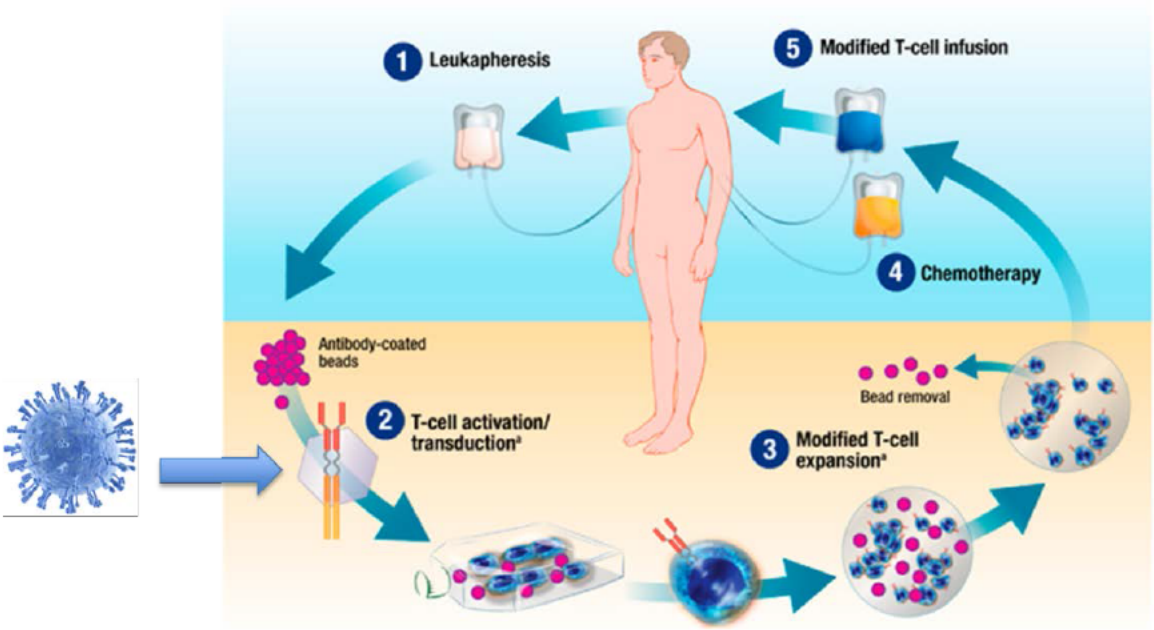


Figure 1. Overview of CAR T cell manufacturing process.
Modified from (Levine, 2015)

4.1.2 General characteristics of CAR T cell therapeutics

Chimeric Antigen Receptor (CAR) T cells are genetically modified antigen-specific immunotherapies that have been reprogrammed to target cells that express a disease-associated antigen, such as a tumor antigen (Eshhar et al., 1993). Multiple clinical studies have investigated CAR T cells that target CD19 for treatment of B cell malignancies (Park et al., 2016). The extracellular portion of the CAR protein usually consists of a murine single-chain antibody fragment (scFv) that recognizes the target antigen (e.g., CD19). The intracellular portion of the CAR protein contains T cell signaling (CD3-ζ) and co-stimulatory domains (e.g., CD28, 4-1BB). Each of the intracellular domains plays an essential role in T cell activation that is required for T cell expansion, persistence of the CAR T cells and anti-tumor activity in vivo (Figure 2). Once the CAR protein engages its target antigen on the cell surface, the intracellular domains promote the CAR T cell expansion and trigger subsequent effector functions to eliminate the disease target cells.

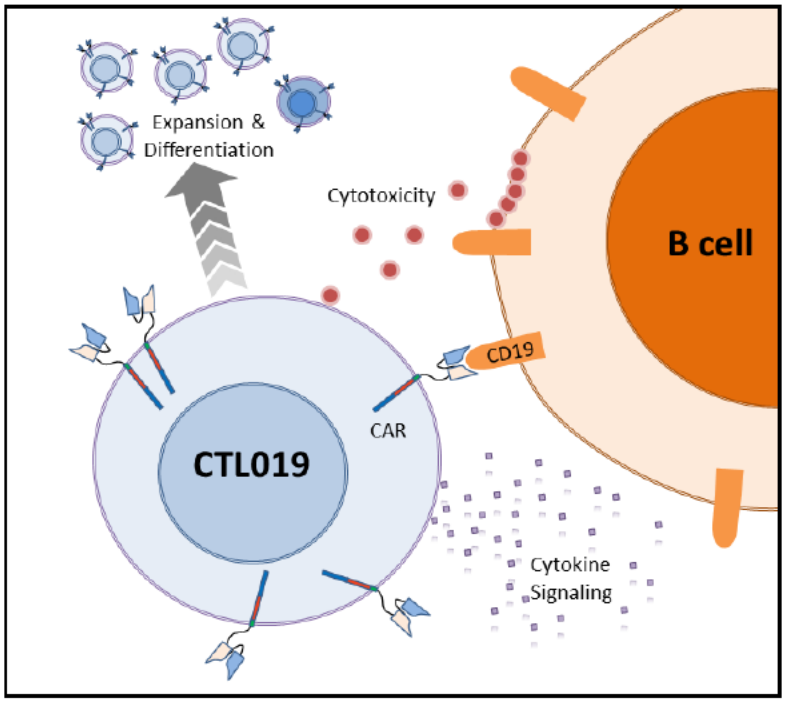


Figure 2. Schematic representation of tisagenlecleucel mechanisms of action.
Upon CAR engagement with CD19 on the surface of a B cell, tisagenlecleucel may produce cytokines for autocrine and paracrine effects necessary for CAR T cell expansion, differentiation, and release of cytotoxic granules.

4.1.3 CAR structure: relationship to safety, function, and CAR T cell mechanism of action

CAR T cell activity is directed by the engineered CAR, which has a modular structure. A schematic structure of tisagenlecleucel is presented in Figure 3 and detailed below. The extracellular domain of tisagenlecleucel is derived from a mouse monoclonal antibody that recognizes human CD19. The spacer and transmembrane domains are derived from human CD8-α, and the intracellular domains are derived from human 4-1BB and CD3-ζ (Milone et al., 2009).

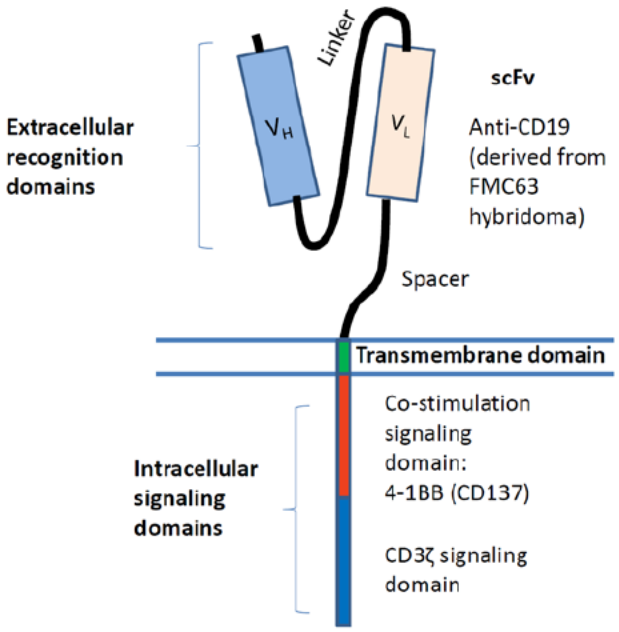


Figure 3. Molecular structure of CAR used for tisagenlecleucel

4.1.3.1 scFv domain

The single-chain antibody fragment (scFv domain) of a CAR provides the targeting function by specifically recognizing a tumor antigen. The specificity of the scFv is a crucial determinant for the CAR T cell safety profile. Therefore, careful attention should be given to antibody selection to minimize possible risks from nonspecific or off-target effects. An in vitro protein array experiment was conducted by the applicant to assess the potential off-target effects of the scFv (FMC63) domain in tisagenlecleucel. CD19 was the only protein identified with a strong binding activity. Given that CD19 expression is restricted within the B-cell lineage, the tisagenlecleucel scFv is considered reasonably safe with respect to off-target activity. However, CD19-directed CAR T cells target CD19 on both B cell tumors and normal B cells. Therefore, B cell aplasia is an expected side effect of tisagenlecleucel and other CD19-directed products, and is mitigated by immunoglobulin replacement therapy.

In addition to scFv specificity, the affinity of scFv binding may play an important role in CAR T cell activation and effector functions, which can impact the safety and activity of the product. The affinity of scFv binding to a tumor antigen is much higher than normal T cell receptor (TCR) binding affinity to tumor antigen epitopes presented by MHC (Chmielewski et al., 2013; Dahan and Reiter, 2012). TCRs recognize digested peptides presented by MHC molecules; in contrast, tisagenlecleucel binds directly to CD19 in its native conformation on the cell surface. Because CAR binding is not restricted by MHC haplotype, the CAR strategy is applicable to a broad range of patients with any MHC haplotype.

scFv is not a native protein and therefore could potentially induce the generation of human anti-mouse antibodies (HAMAs) in patients administered CAR T cell products. Patients with HAMAs may experience serum sickness, as observed in the cases of monoclonal antibody therapies. Pre-existing and treatment induced anti-CAR19 antibody activities were detected in patients. However, no impact on the clinical response rate is evident.

4.1.3.2 Spacer and transmembrane domain

In tisagenlecleucel, the spacer and transmembrane domains are derived from human CD8-α. The spacer provides a flexible link between the scFv and the transmembrane domains. It allows the antigen-binding domain to accommodate different orientations to facilitate antigen recognition. The transmembrane domain provides a physical link between the spacer and intracellular signaling domains. The length and topology of the spacer and transmembrane domains are critical in providing an appropriate steric orientation for specific antigen recognition and subsequent T cell activation.

4.1.3.3 Intracellular signaling domains

The CAR intracellular signaling domains play crucial roles in T cell activation, persistence, and effector functions. Although the CD3ζ chain is adequate for T cell activation, one or more costimulatory domains are also needed to fully activate T cells and to promote CAR T cell persistence (Milone et al., 2009; van der Stegen et al., 2015). These domains are typically derived from the intracellular domains of costimulatory proteins such as CD28 or 4-1BB (CD137). Differences in costimulatory domain function may impact product safety and activity by affecting CAR T cell cytokine production, expansion, cytotoxicity and persistence after administration. The intracellular signaling domains of tisagenlecleucel are derived from human 4-1BB and CD3ζ.

4.1.3.4 Lentivirus vector

Retroviral-based gene therapy vectors (e.g., gammaretroviral, lentiviral) are the predominant choice for CAR transduction due to the stable integration of these vectors, which results in long-term expression of the CAR. Critical vector quality attributes (e.g., titer, potency, purity) directly determine the number of copies stably integrated into the target cells, and therefore to a large extent determine the potency of the CAR T cell product. Due to its criticality in the manufacturing process, the vector encoding the CAR transgene is deemed a critical component, and control of vector lot consistency is critical to minimizing variation in the downstream cell manufacturing steps.

One of the key quality attributes of a vector is the infectious titer, which reflects the ability to transfer the CAR into the target T cells. Therefore, an accurate measure of titer is important for product quality, potency and safety. Lentiviral vectors, like the one used to make tisagenlecleucel, are generally titrated with a standard cell line, such as HEK 293T cells. The vector titers derived from this type of titration may not always reflect the true transduction efficiency in the targeted primary T cells, resulting in an inaccurate titer measurement, which

may contribute to product variability. One strategy to mitigate the risk of an inaccurate titer may be to titer the vector on target primary T cells. Determining vector titers in primary T cells may help minimize the transduction efficiency variations in the transduced cell product.

Potency of the vector is another key attribute that can contribute to product variability. As such, it is important that prior to use for cell transduction each lot of vector be tested for potency using a biologically relevant assay. As with CAR T cell potency, the potency assay for the vector may reflect the relevant biological function of the vector, including the vector encoded CAR. Thus, an assay matrix that includes measures for infectious titer and a relevant assay to measure the CAR activity (as described above) may provide the best assessment of the quality of the vector.

4.1.3.5 Autologous leukapheresis cells

Autologous T cells are the intended cell type in the collected starting leukapheresis material. T cells can possess a variety of anti-tumor activities, including release of cytotoxic granules that directly lyse target cells. T cells can also produce cytokines that provide helper functions and stimulate other immune effectors such as macrophages and B cells. Autologous T cells are a polyclonal mixture of T cells that may include subsets with cytotoxic effector function, helper function and regulatory function.

The composition of autologous cells collected by leukapheresis is not predictable and varies greatly depending on many factors. For patients with B-cell malignancies, the cell composition could vary significantly, depending on such factors as the disease stage, individual genetics, age, infection status, and treatment history. Thus, the starting cells for tisagenlecleucel could have a wide range of cell types (e.g., T cells, B-cell/Blast, monocytes, granulocytes, natural killer cells, erythroid cells (including red blood cells), dendritic cells, platelets). These subset cells may affect the manufacturing process in at least two ways. They may dilute out important critical components for T cell activation and growth, and they may have a direct negative impact on T cell activation, expansion, and transduction efficiency.

As the composition of the starting cells is out of the manufacturer's control, it may be necessary to determine the risk of these contaminating cells and develop strategies to address inter-patient variability in the manufacturing process. Thus, it is necessary that the composition of the starting material be determined prior to manufacturing and that removal or dilution of these cell impurities be monitored. Additionally, since an extremely low number of T cells may impact the ability to produce the final cell dose requirement, a minimal number of T cells may be necessary for CAR T cell manufacturing. Therefore, T cell enrichment steps may be used in the CAR T cell manufacturing process to reduce the variability of the starting material.

4.1.4 Tisagenlecleucel quality attributes that affect safety and biological activity

Tisagenlecleucel is a living biologic that can expand and differentiate, both during the manufacturing process and after administration into patients. The dynamic behavior of cell-derived products can pose challenges to consistent manufacturing of individual lots, to setting meaningful acceptance criteria for lot release, and to defining the clinical dose.

Tisagenlecleucel possesses a unique set of characteristics and quality attributes that have direct impact on the final product safety and potency. Some of these are built into the CAR design (e.g., scFv, signaling domains) and the choice of the lentiviral transfer vector, while other quality attributes are controlled during the manufacturing process (e.g., identity, purity, potency, and safety). We provide a summary of tisagenlecleucel quality attributes in relation to how they may affect product safety and activity in vivo. Vector-related safety issues regarding replication competent virus contaminants and insertional mutagenesis are detailed in Discussion Topic #2.

4.1.4.1 Potency

Potency is defined as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." (21 CFR 600.3(s)). It follows that a robust and biologically relevant potency measure, which reflects the mechanism of action (i.e., recognition of CD19, activation of T cell effector functions through intracellular CAR signaling and costimulatory domains, and elimination of tumor cells (Figure 2), is expected for CAR T cell products. There are a variety of ways to measure T cell activation. In practice it can be challenging to design tests that measure all of the biological activities necessary for CAR T activity in a manner that is both robust and quantitative. Therefore, manufacturers often consider a variety of potential assay designs to measure potency, either as single assays or in combination (an assay matrix).

Potency of tisagenlecleucel is measured by evaluating IFN-γ production in response to tumor antigen-bearing cells. IFN-γ production is considered an indicator of T cell activation and a prerequisite for CAR T cell activity. However, in the clinical trials, IFN-γ production varied greatly from lot-to-lot (Figure 4), making it difficult to correlate IFN-γ production in vitro to tisagenlecleucel safety or efficacy.

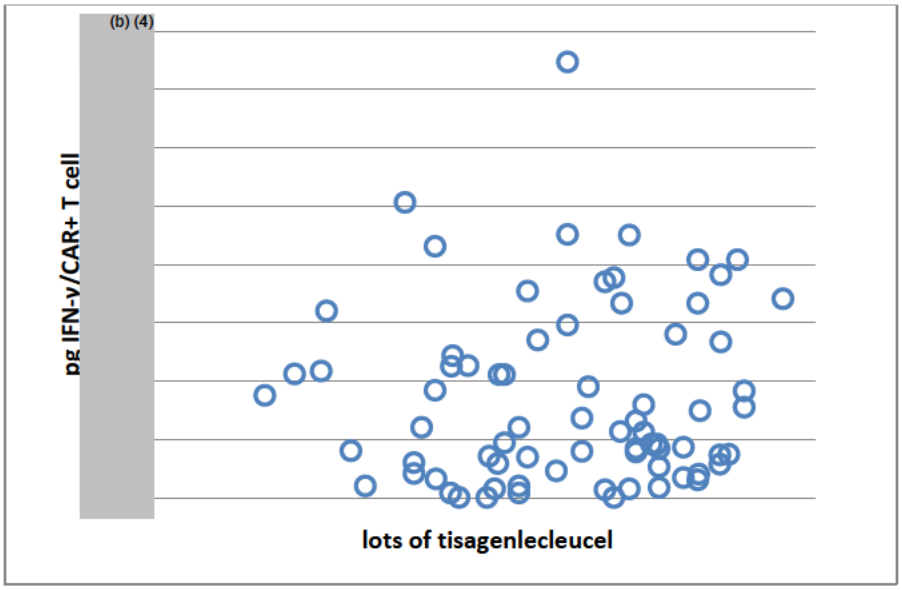


Figure 4. IFN-γ production per transduced cell. IFN-γ produced during co-culture with CD19-expressing cells is quantified as a measure of potency for tisagenlecleucel. (FDA generated)

4.1.4.2 Transduction efficiency: vector copy number and CAR expression

The CAR molecule of tisagenlecleucel is encoded by a lentiviral vector that is introduced into the patient's T cells by a process termed transduction, wherein the vector enters the cell and subsequently integrates into the host genome. The efficiency of the transduction step is evaluated by two complementary measurements: integrated vector copy number (VCN) by qPCR and transduction efficiency by flow cytometry. Measurement of tisagenlecleucel CAR expression includes quantification of both VCN/cell and % CAR positive cells.

Vector copy number (VCN)

VCN estimates the number of vector copies in each transduced cell, which may correlate with the amount of CAR protein on the cell surface. The level of CAR protein expression may affect the T cells' ability to identify and eliminate target cells. For tisagenlecleucel, a good statistical correlation was observed between the vector copy number and percentage of transduced cells by flow cytometry analysis.

VCN for tisagenlecleucel is determined by a qPCR assay that measures the average number of integrated copies of the vector-encoded CAR relative to the total number of cells (Figure 5, blue). Calculation of VCN based on the total cells normalizes the measured copy number according to all cells, not just to transduced cells, and therefore uniformly deflates the number of cells with integrated vectors. Therefore, the data were transformed into a measurement of VCN

per CAR+ cell (Figure 5, red). Both representations of the VCN data indicate that the average transgene integration into tisagenlecleucel CAR+ T cells is variable.

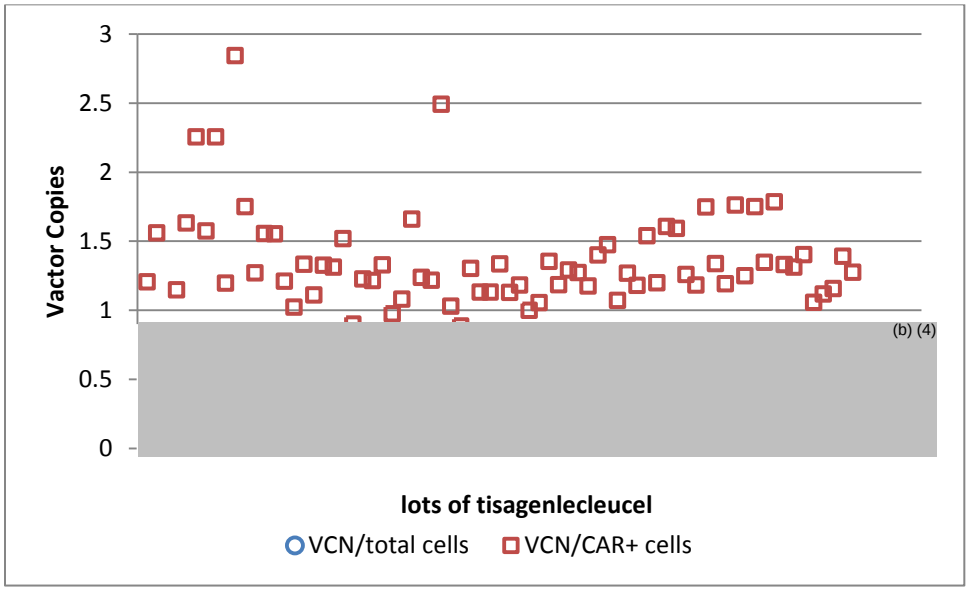


Figure 5. Vector copy number (VCN) for tisagenlecleucel.
Each dot represents one lot of tisagenlecleucel as either VCN/total cells (blue circles) or VCN/transduced cells (red squares) (FDA generated)

VCN can also affect product safety, in that an increased level of insertions per cell may increase the risk for insertional mutagenesis (see Discussion topic #2). Thus, it is critical that VCN be controlled as a critical quality attribute.

CAR expression on cell surface

Transduction efficiency can also be determined by measuring the percentage of T cells that express the CAR on their surface. For tisagenlecleucel, the percentage of T cells that present the CD19-targeting CAR on their surface is quantified by flow cytometry. The antibodies used in the assay are specific to the extracellular antigen-binding domain of the CAR.

The proposed acceptance criteria for commercial lot release allow for a wide range in the number of CAR+ T cells in the final product. There was limited experience with CAR-positive T cell concentrations (b) (4) in the product lots manufactured for use in the clinical trials (Figure 6). Additionally, tisagenlecleucel lots manufactured after process controls were established (February 2016) were consistently manufactured (b) (4) While the dose is calculated based on transduced T cells, the influence of non-transduced T cells on safety and efficacy has not been evaluated. However, non-transduced T cells are not considered to be an impurity and are not expected to pose a significant risk.

Because the active ingredient of the product is CAR-positive T cells, transduction efficiency is used to calculate the final cell dose (number of CAR-positive cells). Therefore, in order to

produce tisagenlecleucel with consistent product quality attributes, it is essential to control the transduction step. This product attribute is typically controlled through the amount of vector used per cell during transduction (i.e., multiplicity of infection (MOI)).

Figure 6. Results of percent CAR-positive T cells in tisagenlecleucel. (FDA generated)

4.1.4.3 Identity

Because tisagenlecleucel is an autologous product, each lot is produced for a single patient. For this reason, the applicant has implemented strictly controlled tracking and segregation procedures, from apheresis to infusion, to ensure proper chain of identity so that the patient receives the tisagenlecleucel product made from his or her own cells. For tisagenlecleucel, identity is further ensured by a number of complementary methods, including qPCR for the CAR gene used in the VCN assay and CAR surface expression by flow cytometry.

4.1.4.4 T cell subsets

The most prevalent cell type in tisagenlecleucel is T cells, (b) (4) Tisagenlecleucel contains CD4 helper and CD8 cytotoxic T cells, both of which may contribute to modulating the anti-tumor immune response or killing tumor cells. Moreover, subpopulations of T cells (i.e., central memory T cells or effector memory T cells) may persist and expand differently in the patient. Predominance of certain T cell subpopulations may be predictive of clinical safety and activity. However, no direct relationships between the T cell composition in tisagenlecleucel and clinical outcomes have been

reported. Currently, T cell subsets are evaluated on each lot of tisagenlecleucel for information purposes, but the results are not used as criteria for release.

4.2 Discussion Point 2: Safety considerations for CAR T cells that are transduced with retroviral vectors (gammaretroviral or lentiviral vectors)

4.2.1 Gene transfer vector for expression of CAR in tisagenlecleucel

Currently, non-replicating retroviral (gammaretroviral and lentiviral) vectors are the most common means for delivering CAR-encoding sequences into T cells, although other methods have also been used. The vector used to manufacture tisagenlecleucel is a self-inactivating lentiviral vector that contains extensively modified sequences from HIV-1. During manufacturing, the vector becomes integrated into the chromosomes of T cells and directs transcription of the tisagenlecleucel CAR using a constitutively-active promoter. Thus, CAR sequences and expression are expected to persist for the life of the transduced T cell, even if the T cell divides.

Although retroviral vectors provide long-term expression of the CAR due to stable integration, they also introduce two potential safety concerns: 1) replication competent retrovirus (RCR) and 2) insertional mutagenesis due to random vector integration into the T cell chromosomes.

4.2.2 Replication competent retrovirus (RCR)

Although RCRs were observed in early generations of gammaretroviral vectors (Donahue et al., 1992), RCRs have not been observed in more recent vector systems, most likely due to improved safety features built into vector design and manufacturing. However, the possibility of RCR generation cannot be entirely excluded. Thus, retroviral-based CAR T cells are rigorously tested throughout the vector and CAR T cell manufacturing steps. During clinical studies, patients are monitored post-administration for possible exposure to RCR following the FDA Guidances for Industry (FDA Guidance for Industry: *Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events*, 2006a; *Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors*, 2006b).

4.2.2.1 Gammaretroviral vectors

Early retroviral vectors were prone to homologous recombination between vector and helper sequences, which could lead to formation of RCR. A Moloney murine leukemia virus (MLV)-derived vector that was contaminated with RCR caused rapidly progressive T cell lymphomas in non-human primates (Donahue et al., 1992). This finding is consistent with the biology of gammaretroviruses, which cause lymphomas in their natural murine host. Retroviral vectors are often engineered with envelope proteins from a different virus that have broadened tropism, which would increase the ability of any RCR to easily transmit to new cells. Given the experience with nonhuman primates mentioned above and the potential broad tropism of RCR, it

is plausible that RCR derived from a MLV retrovirus would be replication competent in human cells and could cause neoplastic transformation.

A number of design features have been introduced into later-generation retroviral vectors to reduce the likelihood of recombination that could lead to RCR generation. Previous vector designs had regions of identical genetic sequences in both the transfer vector and packaging constructs, which increased the likelihood of homologous recombination. Since then, efforts have been made to reduce these homologous genetic regions to limit the recombination events that cause RCR generation. For newer-generation gammaretroviral vectors lacking sequence overlaps between packaging and vector components, no RCRs have been detected during the vector manufacturing process.

4.2.2.2 Lentiviral vectors

Most lentiviral vectors, including the vector used to manufacture tisagenlecleucel, are derived from the HIV-1 genome and pseudotyped with a VSV-G envelope protein in place of the HIV envelope protein. The vector used to manufacture tisagenlecleucel is typical of modern lentiviral vectors in that it is designed with a number of safety features. First, non-essential HIV-1 sequences are not present at all in transfer vector and packaging constructs (e.g., deletion of sequences encoding envelope protein, accessory proteins, Tat and U3 sequences), which makes it unlikely to generate a fully wild-type HIV-1 virus. Second, during vector manufacturing all essential HIV-1 helper sequences and the VSV-G envelope sequences are distributed among multiple plasmids that share little or no sequence homology, which means that RCR can only be formed if there are multiple low-probability recombination events.

4.2.2.3 Testing for RCR

Potential RCRs can be detected using sensitive biological assays that amplify rare RCRs, or using less-sensitive PCR-based assays. To date, no RCRs contamination have been observed for tisagenlecleucel or other lentiviral vectors used in clinical trials, either during vector manufacturing or cell manufacturing. In addition, patient samples can be monitored for RCR (typically using a PCR assay for VSV-G sequences that will only be present if there is an RCR). To date, RCRs have not been observed in patient samples obtained during clinical follow-up in any trial that has used gammaretroviral or lentiviral vectors, including trials with tisagenlecleucel.

Currently, each batch of tisagenlecleucel is tested for RCR using a quantitative PCR (qPCR) for VSV-G sequences. In addition, each batch of vector is tested twice for RCR (once on the vector itself, and once on the end of production cells used to manufacture the vector) using a sensitive culture-based assay. During clinical trials, patient peripheral blood samples were tested for RCR (using VSV-G qPCR) at pre-specified infusion time points after administration of tisagenlecleucel. The applicant has proposed a phase 4 registry that will continue such monitoring for RCR in samples from future patients who receive tisagenlecleucel.

4.2.3 Genotoxicity related to insertional mutagenesis

Integration of retroviral vectors may pose safety risks if the integrated vector adversely affects the host cell genome. Potential mechanisms of insertional mutagenesis include disruption of host tumor suppressor genes, inadvertent activation of host proto-oncogenes and host genome instability. All of these effects could increase the likelihood of genotoxicities, such as clonal outgrowth or neoplastic transformation of transduced host cells.

4.2.3.1 Gammaretroviral vectors

Studies of non-replicating gammaretroviral vectors in animal models have reported leukemia linked to retroviral integration in both mice and in non-human primates (Modlich et al., 2005; Seggewiss et al., 2006). In some studies of transduced hematopoietic stem cells in mice and non-human primates, dominant clones have been found with vector insertions in genes linked to enhanced hematopoietic cell proliferation, although such clones are not necessarily associated with disease (Schmidt et al., 2009).

Genotoxicity caused by insertional mutagenesis has also been observed in clinical trials of gammaretroviral-transduced hematopoietic stem cells. For example, leukemias have been discovered with gammaretroviral vector insertion in or near the LIM domain only 2 (LMO2) gene (Hacein-Bey-Abina et al., 2003). In 2006, FDA published recommendations for the long-term follow-up monitoring of gene therapy recipients for delayed adverse events (FDA Guidance for Industry: *Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events*, 2006a). Since then, additional cases of leukemias and hematologic dysplasias have occurred in multiple trials with a variety of indications (Mukherjee and Thrasher, 2013). Detailed investigation has demonstrated an association of these adverse events with integration of the gammaretroviral vector near proto-oncogenes, including LMO2, myelodysplasia syndrome protein 1 (MDS1), and ecotropic viral integration site 1 (EVI1).

However, integration of a retroviral vector in proximity to a proto-oncogene may not be the sole factor in genotoxicity. Other potential contributing factors may include the therapeutic gene itself, the cell dose and the disease indication. Studies that used gammaretroviral vectors to treat adenosine deaminase deficiency SCID have reported evidence of genotoxicity and clonal expansion (including increased abundance of clones with integrations near proto-oncogenes such as LMO2), but without any negative clinical impact to date (Cooper et al., 2017). Clonal expansion was also observed in clinical trials with gammaretroviral vectors for Chronic Granulomatous Disease (Ott et al., 2006) and Wiskott-Aldrich syndrome (Braun et al., 2014), with progression to leukemia in some cases.

There is a recent report of a lymphoma case 15 years after treatment with a gammaretroviral vector product from the original SCID-X trial in France (Six et al., 2017). The vector was detected in blast cells, and integration site analysis showed expansion of a clone with vector inserted 30 kb from the LMO2 gene, as well as upregulated expression of the LMO2 gene. This

late serious adverse event demonstrates that clonal expansion and malignant transformation can take many years to manifest.

4.2.3.2 Lentiviral vectors

There have been a few reports of lymphomas thought to be due to insertional mutagenesis after integration of HIV-1 virus (Knight et al., 2013), but there have been no reports of such events associated with lentiviral vector integration in 43 gene therapy studies conducted world-wide to date (The Journal of Gene Medicine Gene Therapy Clinical Trials Worldwide, 2017).

The vector used in tisagenlecleucel is a self-inactivating (SIN) lentiviral vector, meaning that it lacks a viral-derived promoter in the LTR region. The HIV-1 LTR promoter is very strong, and therefore SIN lentiviral vectors that lack this promoter have a reduced propensity for activation of nearby proto-oncogenes. This lower risk is borne out by the results of recent clinical trials that have used SIN lentiviral vectors. For example, Wiskott-Aldrich syndrome (WAS) patients who received gene therapy via a self-inactivating lentiviral vector have not, as yet, displayed any signs of genotoxicity (Hacein-Bey Abina et al., 2015), suggesting that the high incidence of leukemia in the previous gammaretroviral WAS gene therapy study may have been a consequence of the vector employed. Similarly, more recent gene therapy protocols for SCID-X1 patients using a SIN lentiviral vector have not shown any insertional mutagenesis-related effects in the 5 years post-treatment (Cavazzana et al., 2016).

Intriguingly, clonal expansion of a predominant integration site has been observed during long-term follow-up of lentiviral gene therapy recipients for β-thalassemia and may have contributed to clinical efficacy (Cavazzana-Calvo et al., 2010).

4.2.3.3 Genotoxicity in T cells

There have been numerous clinical trials with T cells that were transduced with a gammaretroviral or lentiviral vector. Many of these trials used CAR T cells for malignancy indications. To date, there have been no reports of vector-mediated genotoxicity in clinical trials using T cells. The reasons for this lack of vector genotoxicity in T cell products are unknown, but perhaps might be related to the more mature (differentiated) nature of T cells as compared to stem cells (Newrzela et al., 2008). However, gammaretroviral vector-mediated oncogenic transformation of mature T cells has been observed in a susceptible mouse model (Heinrich et al., 2013), and T cell-derived tumors in humans remain theoretically possible.

4.2.4 Retroviral-based risks for tisagenlecleucel

As described above, the vector used for tisagenlecleucel manufacturing is designed to minimize the risk of formation of RCR, and both the vector and the cell product are extensively tested for RCR during the manufacturing process. Regarding the risks of insertional mutagenesis and genotoxicity, clinical long-term follow-up monitoring for clonal outgrowth and vector-mediated delayed adverse events (e.g., secondary leukemias) have not raised any concerns for tisagenlecleucel or for other retroviral-transduced T cell products to date. In addition, during

manufacturing of tisagenlecleucel, the number of integrated vector copies per cell is controlled to minimize the occurrence of T cells that have an excessively high number of vector integrations.

To aid in characterizing the risk of insertional mutagenesis in tisagenlecleucel, the applicant conducted integration site analysis on 12 GMP clinical batches and 2 additional non-GMP batches derived from healthy donor cells. Using an unbiased PCR and sequencing method, the genomic integration site distribution was found to be similar to published reports of other lentiviral vectors, including similar preference for integration in regions of open chromatin, high GC content, and gene activity. For all batches of tisagenlecleucel in this analysis, integration sites were found to be highly polyclonal, with no evidence for integration favoring certain sites, and no evidence for integration near specific oncogenes of concern, such as LMO2.

4.2.4.1 Proposed Post-approval Pharmacovigilance Plan

The applicant has two clinical protocols: proposed for commercial product; CTL019B2401 Phase 4 with a registry and ongoing CCTL019A2205B LTFU for patients who received tisagenlecleucel under the IND. Both the registry and the long-term follow-up study are designed to follow patients for up to 15 years post-treatment, as summarized below.

CTL019B2401 is a prospective registry to assess long-term safety of patients with B lymphocyte malignancies treated with the commercial tisagenlecleucel (Registry). The primary objective is to evaluate adverse events of special interest (AESIs) after treatment with tisagenlecleucel. This will include short-term AESIs and long-term AESIs. The secondary objectives include the following:

- Evaluate other AEs potentially related to tisagenlecleucel therapy
- Evaluate incidence and outcome of any pregnancy
- Assess any hematologic malignancy, secondary malignancy, or B-cell aplasia
- Monitor for presence of RCR (by q-PCR for VSV-G sequences in peripheral blood at pre-specified time points after administration of tisagenlecleucel)Monitor for presence of RCL (by q-PCR for VSV-G sequences in peripheral blood at pre-specified time points after administration of tisagenlecleucel)
- Monitor for presence of RCL (by q-PCR for VSV-G sequences in peripheral blood at pre-specified time points after administration of tisagenlecleucel)

CCTL019A2205B is a long-term follow-up (LTFU) monitoring study in patients exposed to lentiviral-based CD19-directed CAR T cell therapy (LTFU study) on the IND 16130. The primary objective is to assess the safety of long-term exposure to Tisagenlecleucel by evaluating the proportion of patients with events in each of the following categories:

- New malignancies
- New incidence or exacerbation of a pre-existing neurologic disorder,
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder,

- New incidence of a hematologic disorder

The secondary objectives are categorized as following:

- Monitoring the persistence of modified T cells in peripheral blood (via q-PCR for the CAR transgene at pre-specified time points after infusion of tisagenlecleucel).
- Monitoring the presence of RCR by VSV-G q-PCR in peripheral blood at pre-specified time points after infusion of tisagenlecleucel.
- Assessing the long-term efficacy of tisagenlecleucel (proportion of patients who relapse or progress among patients who had not relapsed or progressed at study entry/re-entry; incidence of death; monitor lymphocyte levels).
- Describing the growth, development, and female reproductive status for patients who were aged < 18 years at the time of initial tisagenlecleucel infusion.

5. CLINICAL STUDIES TO SUPPORT EFFICACY AND SAFETY

The primary evidence of safety and effectiveness comes from Study CCTL019B2202 (Study B2202).

Study CCTL019B2202: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia

Sites: 25 Centers in US (13), Canada (2), Europe (8), Japan (1), Australia (1)

All subjects (n=63) in the Efficacy Analysis had tisagenlecleucel manufactured in Morris Plains, New Jersey. Subjects in the Safety Analysis (n=68) include subjects who received tisagenlecleucel manufactured in Morris Plains, New Jersey (n=63) and Fraunhof, Germany (n=5).

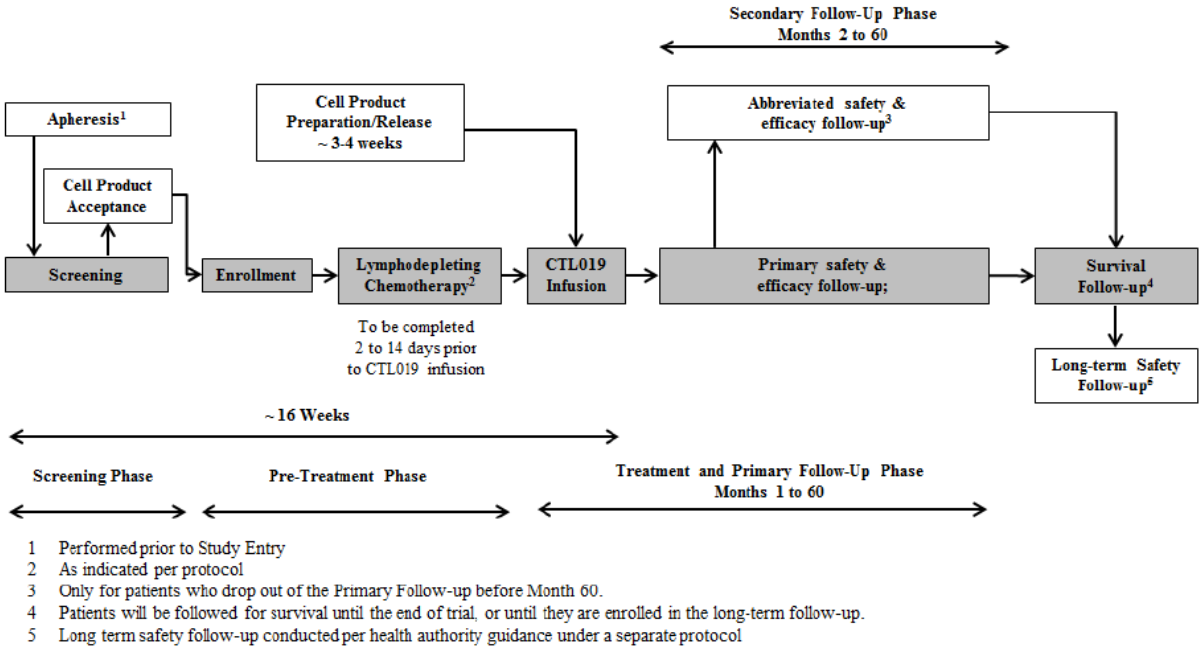
First subject enrolled: April 8, 2015
Last subject enrolled for this review and analysis: August 17, 2016
Data cut-off for efficacy analysis: November 23, 2016

5.1 Study B2202 Design

- Single-arm, multi-center study
- Study 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

Survival and long-term follow-up for genetically modified cell therapy to total of 15 years

Figure 7. Study Design



Source: BLA

The diagram does not include bridging chemotherapy. Please note that the choice of bridging chemotherapy was determined by the local investigator. Sixty-three of the 68 subjects in the safety set received this treatment with US based product after the pheresis material was accepted at the manufacturing site (enrollment) prior to lymphodepletion. Five subjects received product manufactured in Germany so were only considered for safety evaluation as per the updates to the safety and efficacy datasets.

Sample Size

The applicant planned to enroll 50 subjects with 6 months of follow-up following tisagenlecleucel administration.

5.1.1 Objectives

Primary efficacy objective:

- To evaluate the efficacy of tisagenlecleucel therapy as measured by overall remission rate (ORR) during the 3 months after tisagenlecleucel administration; ORR includes CR and CRi, as determined by independent review committee (IRC) assessment.

Key Secondary efficacy objectives:

- Evaluate the percentage of subjects 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 subjects who receive tisagenlecleucel (FAS for IEAS – see below for definition).

Secondary Objectives:

- To evaluate the percentage of subjects who achieve CR or CRi at Month 6 without stem cell transplant (SCT) between tisagenlecleucel infusion and Month 6 response assessment.
- To evaluate the percentage of subjects who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment.
- To evaluate the duration of remission (DOR).
- To evaluate the relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS).
- To evaluate the response at Day 28 +/- 4 days
- To evaluate the safety of tisagenlecleucel therapy as measured by type, frequency and severity of adverse events and laboratory abnormalities.

5.1.2 Eligibility criteria

5.1.2.1 Inclusion criteria (key):

- Relapsed or refractory pediatric (3-21 years at screening) B-cell ALL.
    - Relapse is 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 is defined by not achieving an initial CR after 2 cycles of a standard chemotherapy regimen (primary refractory). Subjects who were refractory to subsequent chemotherapy regimens after an initial remission were considered chemorefractory.

- Subjects with Ph+ ALL are eligible if they are intolerant to or have failed 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 SCT
    - Declined allogeneic SCT 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.

5.1.2.2 Exclusion criteria (key):

- 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 CNS disease (CNS 2 disease [CSF containing blasts, but < 5 WBCs/microliter] subjects were eligible)

5.1.3 Treatment and study drug administration schedule

5.1.3.1 Apheresis:

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

5.1.3.2 Bridging chemotherapy:

Investigator choice after apheresis product accepted at manufacturing site

5.1.3.3 Lymphodepletion (LD):

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)

5.1.3.4 Tisagenlecleucel infusion:

- Given 2-14 days after completion of LD

- Eligibility Criteria for the infusion
  - 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 by physical exam.
  - 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
    - Subject requiring concomitant medications listed in exclusion criteria at screening
    - Recent SCT
    - If > 4 weeks from LD, may require repeat LD chemotherapy if white blood count (WBC) > 1000 cells/µL (microliter).
    - Change in cardiac status from screening
    - Positive pregnancy test

- Tisagenlecleucel infusion:
  - 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 subject met infusion criteria
  - Dose was weight-based:
    - For subjects ≤ 50 kg: 0.2 to 5 x 10e6 viable transduced T cells /kg body weight
    - For subjects > 50 kg: single dose of 1 to 2.5 x 10e8 viable transduced T cells

5.1.3.5 Short and long-term follow-up phases:

- Subjects were followed:
  - For the first 28 days: 2-3 visits per week if outpatient; daily if inpatient
  - Monthly for the first 6 months
  - Every three months: Months 6-24

- Every 6 months: Years 3-5
- Then yearly for 15 years on separate long-term follow-up study

5.1.4 Efficacy

5.1.4.1 Primary efficacy endpoint

The pre-specified primary efficacy endpoint tested the null hypothesis of the ORR being less than or equal to 20% against the alternative hypothesis that the ORR was greater than 20% at an overall one-sided 2.5% level of significance. The study met its primary objective if the lower bound of the 2-sided 95% exact Clopper Pearson confidence intervals (CI) for ORR was greater than 20%.

5.1.4.2 Key secondary efficacy endpoint

The key secondary objective of the study is to evaluate the percentage of subjects who received tisagenlecleucel and achieved a BOR of CR or CRi with an MRD-negative bone marrow by central analysis using flow cytometry during the 3 months after tisagenlecleucel administration.

5.1.4.3 Analysis populations

- Screened Set: All subjects who signed an inform consent and passed screening criteria.
- Enrolled Set: All subjects who meet all inclusion and exclusion criteria and for whom the leukapheresis product is accepted by the applicant. The applicant submitted efficacy data from 88 enrolled/68 FAS subjects based on the data cut-off date of November 23, 2016. Five subjects from the enrolled sets had tisagenlecleucel manufactured at a non-US site and therefore excluded from the enrolled set for primary efficacy analysis.
- Full Analysis Set (FAS) or the final efficacy analysis set: All subjects who were assigned to and received tisagenlecleucel infusion
- Interim Efficacy Analysis Set (IEAS): The protocol specified definition was based on the first 50 subjects who fit the FAS definition and for whom the product was manufactured at the US facility. As described above for the purposes of the interim analysis of B2202 results provided in this BLA, the modified IEAS population consisted of 63 subjects after five subjects (for whom the tisagenlecleucel was produced at a non-US site) were excluded from the 68 subjects for whom efficacy data was submitted.
- Safety Set: All subjects who received tisagenlecleucel including the 5 subjects for whom the product was manufactured at the non-US site.
- Per Protocol Set (PPS): Subjects who met the FAS and IEAS and were not considered to have had major protocol deviations. Major protocol deviation was defined as follows:
  - No diagnosis of ALL at baseline or incomplete or missing documentation of disease.
  - Do not meet criteria with regard to number and type of prior treatments as specified in the screening criteria.
  - Doses that are below the dose ranges specified above.

5.1.4.4 Independent review committee (IRC)

The applicant appointed an IRC to review disease response assessments. There were three core members external to the applicant with clinical expertise in the management of patients with ALL. The IRC was to report the following efficacy results based on the protocol specified efficacy assessments (see below).

5.1.4.5 Efficacy endpoint assessments:

Efficacy assessments mandated at screening and Month 1.

- Bone marrow aspirate and biopsy for blast cell count and MRD assessments. Additional evaluations were recommended at 3 and 6 months from tisagenlecleucel infusion.
- Peripheral blood for blast, neutrophil and platelet counts. Additional mandatory evaluations were required monthly for 6 months, every 3 months thereafter until 2 years and every 6 months thereafter until 5 years from tisagenlecleucel infusion.
- CSF assessment/Lumbar puncture. Additional assessments were performed as clinically indicated.
- Peripheral blood flow cytometry for B and T cell count, CD19 and tumor assessment. Additional evaluations were mandatory weekly from infusion to Month 1 and every 3 months until 1 year and annually thereafter for 5 years from tisagenlecleucel infusion.
- Assessment for extramedullary disease by physical exam and CNS symptoms. Additional mandatory evaluations were required monthly for 6 months, every 3 months thereafter until 2 years and every 6 months thereafter until 5 years from tisagenlecleucel infusion

Optional efficacy assessments

- Lymph node biopsy and aspirates and CNS Imaging by CT or MRI scans were performed as clinically indicated.

Definition of Response

The definition of CR, CRi, no response (NR) and unknown response is provided in APPENDIX 1. Best response will be assigned according to the following order:

- CR
- CRi
- NR
- Unknown

In order for the best ORR to be categorized as CR or CRi, a confirmatory evaluation was required at 4 weeks after the first CR or CRi determination. This confirmatory evaluation

required assessment of the peripheral blood and assessment for extramedullary disease as described above.

Duration of remission (DOR): defined as the duration from the date when the response criteria of CR or CRi are first met to the date of relapse or death due to underlying cancer. If a subject 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 progression at the data cut-off date
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (includes SCT)
- Event after missing at least two scheduled disease assessments

Subjects who receive SCT while in response to tisagenlecleucel will be censored at date of the transplant. In addition, death due to reason other than ALL will be considered as a competing risk event to other events of interest (relapse or death due to ALL).

Event-free survival (EFS): the time from date of first tisagenlecleucel infusion to the earliest of the following:

- Death from any cause after remission
- Relapse
- Treatment failure: defined as no response in the study and discontinuation from the study due to any of the following reasons:
  - Death
  - Adverse event (including abnormal laboratory values or abnormal test procedure results)
  - Lack of efficacy or progressive disease
  - New anticancer therapy

Overall survival (OS): the time from date of first tisagenlecleucel infusion to the date of death due to any reason.

5.1.5 Safety

5.1.5.1 Definition of safety terms

Adverse event

- Adverse Events were graded as Grade 1 through 5, with Grade 5 being death. A serious adverse event was any untoward medical occurrence regardless of grade that resulted in death, was life-threatening, required or prolonged hospitalization, resulted in significant disability/incapacity, or was a congenital anomaly/birth defect.

- Treatment-emergent event: any adverse event that occurred after the administration of the first dose of study drug and through 30 days after the last dose, or any event that was present at baseline and continued after the first dose but worsened in intensity.
- Serious adverse events was defined as follows:
    - Is fatal or life-threatening
    - Results in persistent or significant disability/incapacity
    - Constitutes a congenital anomaly/birth defect
    - Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
    - Requires inpatient hospitalization or prolongation of existing hospitalization with the exception of hospitalization for elective purposes or routine monitoring for study purposes.
    - Positive RCL test result
    - Vector insertion site sequencing result with a mono-or oligoclonality pattern or in location near a known human oncogene
    - New malignancy (T cell & non T cell), other than primary malignancy
    - PML
- Adverse events of Special Interest for safety analyses included TLS, febrile neutropenia, CRS, infection, transient neuropsychiatric events lasting greater than 28 days.
- CRS for safety analyses included fever, myalgia, hypotension, dyspnea, tachypnea, capillary leak syndrome, hypoxia, organ failure and acute respiratory distress syndrome.
- Neurotoxicity: The analyses for neurotoxicity did not include all neurotoxicity, but focused on serious neurotoxicity events related to encephalopathy, delirium, focal deficits, and seizures

5.1.5.2 Grading criteria for CRS

- For details of the Penn Grading Criteria please refer to APPENDIX 2. This grading criteria 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.

5.1.5.3 Grading criteria for neurotoxicity

- Based on CTCAE v.4.03

5.1.5.4 Management of CRS

- For details of the CRS treatment algorithm, please refer to APPENDIX 2.

- Notable aspects of CRS management that are different from the management of hemodynamic instability in the ICU setting, include the requirement for administration of

tocilizumab, and the introduction of high-dose corticosteroids and siltuximab in a timed and sequential order when each of the prior medications for the treatment of hemodynamic instability fails.

5.1.5.5 Management of neurotoxicity

The management of neurotoxicity was supportive and included corticosteroids and airway protection.

5.1.5.6 Management of infusion reactions

The management of infusion reactions was part of the CRS treatment algorithm.

5.2 Study B2202 Results

5.2.1 Subject disposition

Table 3. Subject Disposition

Enrolled	88 subjects
Discontinued prior to tisagenlecleucel infusion	**16 subjects** · 15 subjects were to receive product from MP · 1 subject was to receive product from FH
Tisagenlecleucel infusion pending	**4 subjects** · 0 subjects were to receive product from MP · 4 subjects were to receive product from FH
Tisagenlecleucel infused	**68 subjects** · 63 subjects received product from MP · 5 subjects received product from FH

*MP: Morris Plains, New Jersey manufacturing site; FH: Fraunhof, Germany manufacturing site

Of the 16 subjects who did not receive tisagenlecleucel, there were 7 manufacturing failures (MF), 3 adverse events (AEs) and 6 deaths per the applicant in the Safety Set.

5.2.2 Demographics with prior treatment history

Table 4. Baseline characteristics and demographics of study subjects

Category	Subcategory	Enrolled Set* N=88	Safety (Full) Analysis Set^ N=68
Sex - n (%)	Male Female	48 (55) 40 (45)	38 (55.9) 30 (44.1)

Category	Subcategory	Enrolled Set* N=88	Safety (Full) Analysis Set^ N=68
Age	Mean (SD) Median Min-Max	12.1 (5.4) 11.5 3-27	12.2 (5.3) 12 3-23
Age category – n(%)	3-<10 ≥ 10 to < 18 ≥ 18	37 (42) 35 (40) 16 (18)	28 (41.2) 28 (41.2) 12 (17.6)
Race - n (%)	White Asian Other	65 (74%) 10 (11%) 13 (15%)	51 (75) 6 (9) 11 (16)
Ethnicity – n (%)	Hispanic or Latino Other	17 (19) 71 (81)	14 (21) 54 (79)
Performance Status at Baseline	Mean (SD) Median (min, max)	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)
Number of Previous CRs	N Mean (SD) Median (Min-Max)	88 2.3 (1.4) 2 (0-6)	68 3.2 (1.47) 3 (1-8)
Time since initial Diagnosis (months) to first relapse N* (%)	N Mean (SD) Median (Min-Max)	81 32.2 (15.5) 31.2 (1-70)	63 33.3 (16.6) 33.1 (1-70)
Time from Diagnosis to first relapse N (%)	N < 18 months 18-36 months >36 months	81 17 (21.0) 32 (39.5) 32 (39.5)	63 14 (22) 21 (34) 28 (44)
Time from most recent relapse to tisagenlecleucel infusion - months	N Mean (SD) Median (Min-Max)	Not defined for subjects enrolled but not infused	62 4.1 (2.73) 3.4 (1.5-13.8)
Number of Prior HSCT performed	0 1 2	36 (41%) 45 (51%) 7 (8%)	28 (41%) 35 (51%) 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)

*Data not available for all subjects in enrolled set. ^ subjects treated with tisagenlecleucel made in US

(Source: FDA statistical review, clinical review, and BLA)

5.2.3 Efficacy results

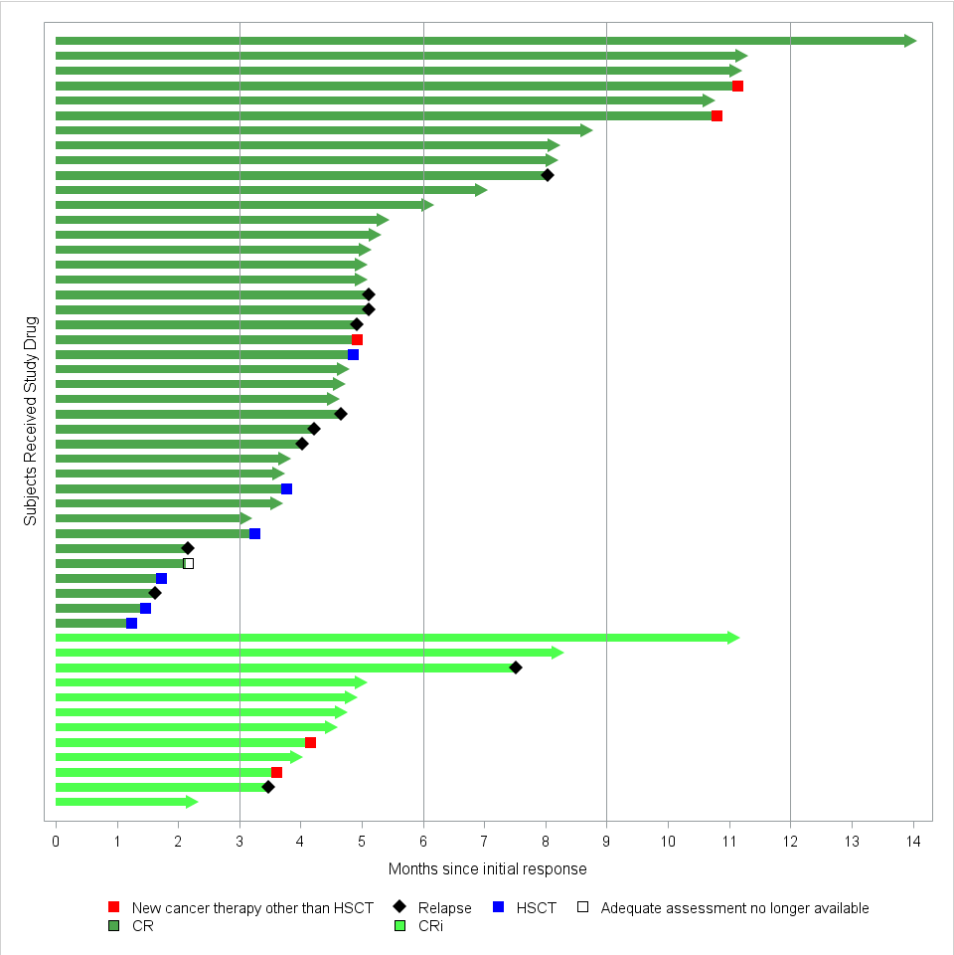
5.2.3.1 Analysis of overall remission rate (ORR), the primary endpoint, and best overall response of CR/CRi with an MRD negative bone marrow, the key secondary endpoint

Table 5. ORR Results for the Efficacy Analysis Set Primary Endpoint (ORR) and Key Secondary Endpoint (BOR, MRD negative)

	Efficacy Analysis Set: Primary Endpoint (n=63) n (%)	**Efficacy Analysis Set: MRD-negative (n=63) n (%)**	**Efficacy Analysis: CR/CRi on D28 only (n =63) n (%)**
ORR (95% CI)	52 [82.5% (CI 70.9, 91.0)]	52 (82.5%)	57 (90%)
CR	40 (63%)	40 (63%)	41 (65%)
CRi	12 (19%)	12 (19%)	16 (25%)
NR/UNK	11 (17.5%)	11 (17.5%)	6 (10%)

5.2.3.2 Duration of response

Figure 8. Analysis of Duration of Response (DOR)



Complete Remission and durability of response

The above swimmer's plot affirms that tisagenlecleucel subjects sustained clinically meaningful remissions. In Study B2202, 11 of the 52 subjects who achieved a CR+ CRi relapsed after tisagenlecleucel prior to the data cut-off date, before any new cancer therapy. In addition, two more subjects relapsed after receiving both tisagenlecleucel and new cancer therapy. Twenty-nine of the 52 subjects were still in remission at the last assessment before the data cutoff. Twelve of the 52 subjects were censored for DOR as follows: 6 subjects for SCT, 5 subjects for new cancer therapy, and 1 subject for adequate assessment no longer available. The estimated relapse-free rate among responders at Month 6 was 75.4% (95% CI: 57.2, 86.7).

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. The 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.

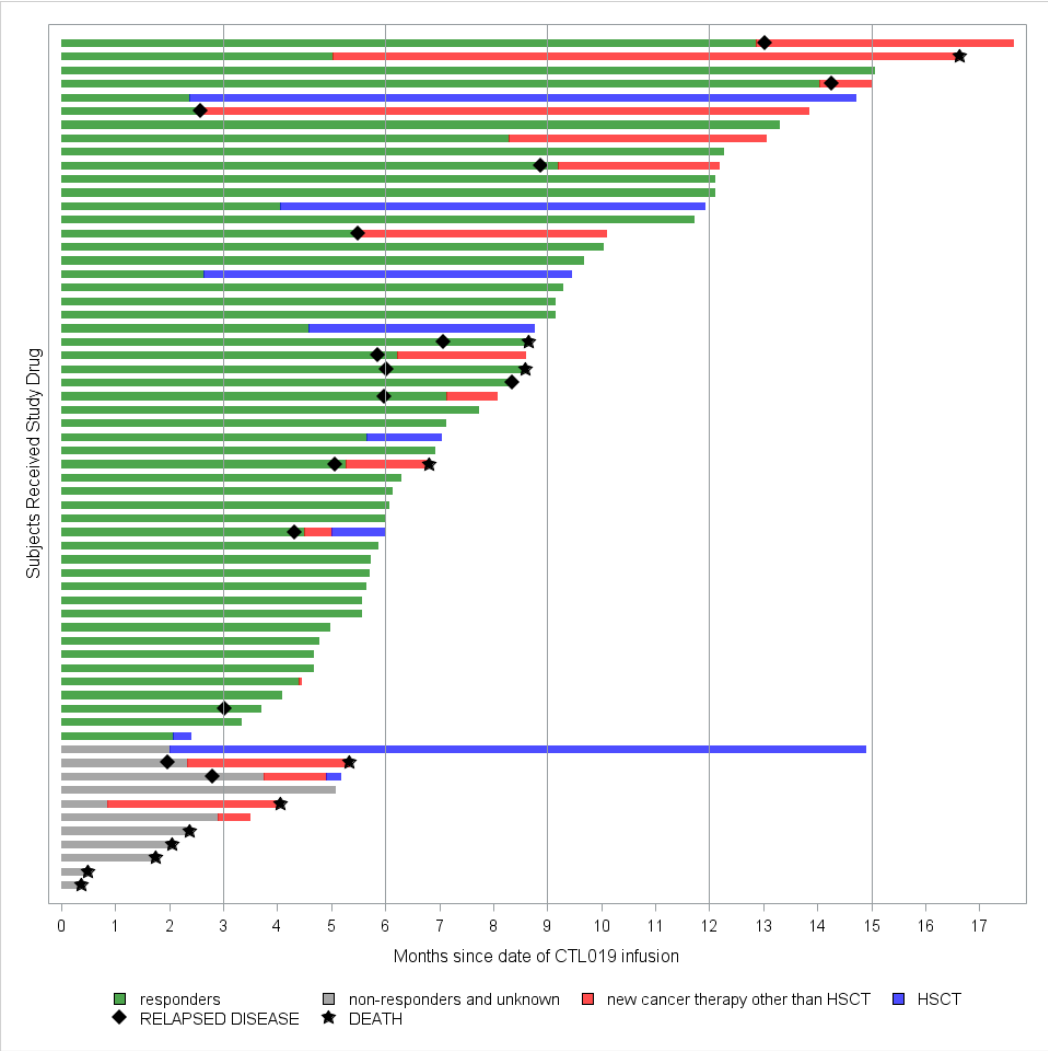
The median follow-up time for DOR was 4.8 months (Range: 1.2 – 14.1 months). The median DOR was not reached.

5.2.3.3 Event-free survival (EFS)

The median follow-up for EFS was 5.6 months (Range 0.03-15.1). Of the 63 subjects in the IAES set, 20 subjects (31.7%) had an event. The median EFS has not yet been reached.

5.2.3.4 Overall survival

Figure 9. Overall Survival for Study B2202



Source: FDA Statistical Reviewer

A total of 11 subjects (17.5%) died after tisagenlecleucel infusion. Seven subjects received HSCT in remission after receiving tisagenlecleucel. Fourteen subjects went on to other chemotherapy without HSCT. No deaths occurred from CRS.

5.2.3.5 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 subjects 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 subjects, and 63 subjects were infused with tisagenlecleucel manufactured in the U.S. facility. A total of 52 subjects (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 subjects (63%) had a best response of CR within the first 3 months after infusion, and 12 subjects (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.

5.2.4 Safety results

The primary safety analysis was performed on the findings from Study B2202, including 68 subjects who received one dose of tisagenlecleucel. Sixty-three subjects received product manufactured in Morris Plains, New Jersey and 5 manufactured in Fraunhofer, Germany

Safety was evaluated based on recorded adverse events, physical examinations, and clinical laboratory assessments. If a subject experienced multiple episodes of a single adverse event, the greatest severity and strongest investigator assessment of relation to study drug were assigned to the adverse event.

Baseline demographics for Study B2202 are described in Table 4.

5.2.4.1 Drug exposure

Bridging Chemotherapy:
In the Updated Safety report for Study B2202, 58/68 or 85.3% of the subjects received chemotherapy between their pheresis and lymphodepletion. The bridging therapy included multiple chemotherapeutic agents (76.5%) including methotrexate (intrathecal and oral), corticosteroids (dexamethasone and prednisone; anthracyclines (16%); monoclonal antibodies (7%), including one subject who received inotuzumab; asparaginase (34%); etoposide (35%); cytarabine (59%); and vincristine (52%).

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

Of the 68 subjects in the safety set, 64 received fludarabine (n=1) or fludarabine + cyclophosphamide (n=63), one subject received the alternative cytarabine regimen and 3 subjects (4%) received no lymphodepletion.

Tisagenlecleucel

For protocol specified dose and regimen, please refer to Treatment and Study Drug Administration Schedule. To summarize, the dose of tisagenlecleucel was weight-based in subjects ≤ 50 kg: 2 to 5 x 10e6 viable transduced T cells /kg body weight (range 0.2-5 viable transduced cells x 10e6/kg) with a maximum dose of 2.5 x 10e8 viable transduced T cell for subjects > 50 kg (range: 0.1 - 2.5 x 10e8 viable transduced T cells).

Table 6. Dose Administered for the Safety Set (FAS)

	Safety Set
Description	**Study B2202 N=68 n (%)**
Below Target Range	5 (7.4)
Within Target Range	61 (89.7)
Above Target Range	2 (2.9)
Transduced viable T cell dose infused (10e8 cells)	
Mean (SD)	1.15 (0.622)
Median	1.00
Min-Max	0.03-2.60
Weight-adjusted transduced viable T cell dose infused (10e6 cells/kg)	
Mean (SD)	2.88 (1.211)
Median	3.00
Min-Max	0.2-5.4
Total Cells Infused (10e8 cells)	
Mean (SD)	5.58
Median	4.71
Min-Max	0.2-20.0

Source: BLA; SCE Addendum 1 Appendix 2-Table 1-2.1

As noted in Table 6, the dose of tisagenlecleucel infused to the majority of the subjects (89.7%) on Study B2202 was within the target range. The applicant had 7 manufacturing failures on Study B2202 in the products manufactured at the Morris Plains, New Jersey plant. One manufacturing failure occurred at the Fraunhof, Germany plant. The remaining subjects with failed production went off-study with no additional attempt at manufacturing an acceptable product.

5.2.4.2 Study safety population and subject disposition

A total of 107 patients were screened; 88 subjects were enrolled into the study. Among enrolled subjects, a total of 68 subjects constitute the FAS that received tisagenlecleucel.

Subject Disposition:
Eighty-three of the 88 subjects had or were intended to have product manufactured in Morris Plains, New Jersey. Sixteen subjects discontinued prior to tisagenlecleucel infusion (18%), 6 due to death (ALL (n=3), sepsis (n=1), respiratory failure (n=1), and fungus (n=1)), 7 due to manufacturing failures (with concurrent AE and deaths), and 3 due to adverse events (infections (n=2), GVHD (n=1)). Four subjects (with product from Fraunhof, Germany) are awaiting infusion. Forty-nine (56%) subjects remain in study follow-up. Nineteen subjects discontinued follow-up, 7 subjects died; 5 subjects failed to respond or relapsed; 5 subjects went on to new therapy; and 2 subjects withdrew consent for follow-up.

5.2.4.3 Adverse events after tisagenlecleucel

The incidence of adverse events after tisagenlecleucel administration in Study B2202 is described in Table 15 in APPENDIX 2. A total of 68 subjects were exposed to tisagenlecleucel, and all (100%) had at least one adverse event (grades 1-5). Of these, 18 subjects (26.5%) experienced Grade 3 events, and 40 subjects (58.8%) experienced Grade 4 adverse events.

For information regarding the Penn CRS grading criteria and treatment algorithm, please refer to APPENDIX 2.

5.2.4.4 Serious adverse events

Table 7. Serious Adverse Events that Occurred in >5 % of Subjects post-infusion with tisagenlecleucel.

Serious Adverse Events	tisagenlecleucel n*=68 (%)
Cytokine release syndrome	43 (63.24%)
Febrile neutropenia	14 (20.59%)
Hypotension	8 (11.76%)
Acute kidney injury	5 (7.35%)
Fever	5 (7.35%)
Hypoxia	4 (5.88%)

*subjects [Source: JReview SAE]

As noted above, the most common serious adverse events are CRS and its components fever, hypotension, acute kidney injury, and hypoxia. Due to the bridging chemotherapy and lymphodepletion, 21% of the subjects were also noted to have febrile neutropenia immediately after tisagenlecleucel. Cytopenias persisted after the infusion, past the normal expected recovery time. However, with a small number (n=2) of subjects who did not receive lymphodepletion, it is difficult to establish the contribution of tisagenlecleucel to the neutropenia. In addition, cytopenias and resultant complications are anticipated in this heavily pre-treated group of subjects.

5.2.4.5 Adverse events of special interest

Table 8. B2202: Safety: Study B2202 Adverse Events of Special Interest within 8 weeks after infusion of tisagenlecleucel (n=68)

Study B2202 N=68	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Patients with at least one event	23 (34)	28 (41)	62 (91)
CRS	14 (21)	18 (27)	53 (78)
Febrile Neutropenia	23 (34)	2 (3)	25 (37)
Hematopoietic cytopenia not resolved by Day 28	10(15)	12 (18)	25 (37)
Infections	16 (24)	2 (3)	29 (43)
Transient neuro-psychiatric events	10 (15)	0	30 (44)
Tumor Lysis Syndrome	3 (4)	0	3 (4)

*source: Case Report Forms; ADSL, AESI

The applicant identified adverse events of special interest based on the mechanism of action, the preclinical data, and emerging clinical data. These adverse events were important in the context of management of the clinical syndrome of CRS and assessment of risks.

Cytokine Release Syndrome (CRS):

On Study B2202, 53 of 68 (78%) subjects treated with tisagenlecleucel (Table13) experienced CRS. 32/68 (47%) of subjects 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.
- Median duration of CRS was 8 days.

Serious morbidities associated with CRS (n=68):

- Seven subjects (10%) required dialysis for a mean of 11 days.
- There was no correlation between the dose of tisagenlecleucel cells and the grade of CRS.
- Infections occurred in 12 subjects during CRS; these infections included seven episodes of sepsis, one CNS infection, and 7 other infections.
- Forty-nine (72%) subjects had fevers, with a mean duration of 8 days and a range of 1-36 days.
- Thirty-one (46%) Study B2202 subjects with severe CRS were admitted to the ICU, with a mean ICU stay of 11 days (range 1-34 days).
- Ten (15%) subjects required ventilatory support for a mean of 8.5 days (range 4-19 days)
- 35 (51%) subjects had documented hypotension
  - 17 (25%) subjects required high – dose vasopressor support
- During CRS, subjects developed a coagulopathy marked by hypofibrinogenemia – Grade 3 in 14 subjects and Grade 4 in 18 subjects. One subject died after recovery from CRS, with death due to ongoing coagulopathy with intracranial hemorrhage.
- In general, cytokine levels and inflammatory markers correlated with the grade of CRS. The highest levels of IL-6, CRP, and ferritin were in Grade 3 and Grade 4 CRS.
- In the Study B2202 subjects, tumor burden was assessed at baseline evaluation (before bridging and lymphodepletion) as low < 50% (n=23) versus high ≥ 50% (n=45) BM involvement. Seventeen subjects with low tumor burden developed CRS; 6 developed Grade 3 or 4. Thirty-six subjects with high tumor burden developed CRS, 26 developed Grade 3 or 4 CRS. There was a trend toward correlation between tumor burden and severity of CRS.
- To date, with small numbers, presence of CRS does not correlate with ORR.

In the Safety Analysis Set, 26 (38%) subjects received tocilizumab for the management of CRS. The onset of CRS often coincides with the initial expansion of tisagenlecleucel, followed by a peak in cytokines such as interleukin-6 (IL-6). Subjects with grade 3/4 CRS received tocilizumab as the tisagenlecleucel cells were achieving maximal expansion; tocilizumab administration was associated with cessation of CRS in most cases.

Table 9. Treatment of CRS on Study B2202

Study B2202 CRS (All Grades)	N=53
Systemic Anticytokine given [n (%)]	26 (49)
Tocilizumab • 1 dose • 2 doses • 3 doses	 26 (49) 16 (30) 7 (13)

Study B2202 CRS (All Grades)	N=53
Siltuximab	5 (9)
Corticosteroids	14 (26)
Other	2 (4)

Overall, the incidence of Grade 3/4 CRS was 47%. There were no mortalities attributed to CRS with symptomatic improvement to therapy with tocilizumab and other supportive care measures recommended in the treatment algorithm in the protocol. 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 further discussion by the Committee with regard to the post-marketing considerations to minimize risk to subjects.

Neurotoxicity:
Neurotoxicity was reported in 44% (n=30) of the subjects who received tisagenlecleucel. Ten (15%) of those subjects had Grade 3 neurotoxicity. In general, neurologic events were concurrent with CRS but 6 occurred after CRS. Resolution of symptoms occurs over weeks and can lag behind CRS recovery. There were no reported cases of cerebral edema with tisagenlecleucel. Treatment for neurotoxicity has been symptomatic treatment includes close monitoring and observation to assure the airway is maintained, seizure prophylaxis, and corticosteroids (dexamethasone).

Additional isolated adverse events of special interest that are relevant to the safety assessment included:

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 as the CAR T cells are being administered. Like primary HLH, subjects can be pancytopenic, have low fibrinogen, hemophagocytosis in bone marrow (BM), spleen, and/or lymph nodes. It occurs when CRS is expected so difficult to discern. In this protocol, there were 5 subjects reported in the Safety database to have HLH. Two subjects (1100 001 and 1451 003) had the most consistent clinical profile.

Infections within 8 weeks after tisagenlecleucel administration
Twenty-nine subjects on Study B2202 developed infections in the first 8 weeks after tisagenlecleucel administration. Sixteen 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. UPN 1100-002, the index case, developed encephalitis consistent with Human Herpes Virus 6 (HHV6). One other case of viral encephalitis was noted on Study B2202 (UPN 1351-003), with HHV6 and CMV detected in cerebral spinal fluid. Another case of systemic HSV and HHV6, concurrent with fungal sepsis, was found in

UPN1404-003. This case was fatal. The subject was also pancytopenic. Subjects on Study B2202 experienced profound neutropenia as well as acquired hypo/agammaglobulinemia and required supplemental IV IgG.

Prolonged Cytopenias

Prolonged neutropenia and thrombocytopenia (after 30 days) has been noted after treatment with tisagenlecleucel. Twenty-five of the 52 responders to tisagenlecleucel had incomplete hematologic recovery. Neutropenia was prolonged but resolved over time. Grade 3 poor recovery occurred in 10 subjects (14.7%), and Grade 4 occurred in 12 (17.6%) subjects. Recovery was achieved by 6 months with improvements noted by 3 months.

Cardiac Disorders:

Per the clinical study report, in an analysis of the initial 62 subject safety set, 20 had cardiac events. Grade 3 left ventricular dysfunction (LVD) was noted in three subjects (one each of Grade 2, 3, 4 CRS) and one of these subjects with LVD also had biventricular failure, mitral incompetence and had Grade 4 cardiac failure in conjunction with Grade 4 CRS. Arrhythmias and congestive heart failure (CHF) are not commonplace in a pediatric population. However, this population (r/r ALL) has a history of prior exposure to anthracyclines as well as prior HSCT in 60% of the subjects on Study B2202 which are considered in standard-of-care treatment for relapsed pediatric ALL. CHF generally developed with severe CRS; as noted above and improved after resolution of the CRS.

B cell aplasia/Acquired hypogammaglobulinemia

As noted in the background section, tisagenlecleucel not only kills pre-B ALL cells, it also kills normal B cells because they are CD19+. As a result, successful treatment with tisagenlecleucel renders the trial participants with acquired hypogammaglobulinemia. Subjects have been maintained on supplemental treatment with intravenous gamma globulin (IV IgG) post-tisagenlecleucel. The tisagenlecleucel CAR cells persist, and so does the need for IV IgG.

5.2.4.6 Clinical test results

There were clinically important laboratory values associated with tisagenlecleucel in Study B2202. Prolonged cytopenias were noted in 37%. The clinical chemistry abnormalities were primarily Grade 1/2. These laboratory values were part of the clinical spectrum of safety concerns previously described in this document. Adverse events and serious adverse events after tisagenlecleucel are described above and in APPENDIX 3. These include renal, hematologic, and organ toxicity.

5.2.4.7 Deaths

Pre-Infusion: 12

- 6 due to ALL; 5 due to infections; 1 due to respiratory failure

Post-Infusion: 11

- 2 within 30 days
  - 1 from ALL
    - B2202 1100-001
    - 11 year-old girl, pancytopenic pre-treatment
    - Tisagenlecleucel infusion on Day 1
      - On broad-spectrum antibiotics, antivirals, anti-fungals
      - Develops hypercalcemia and disseminated intravascular coagulation
      - Progression of ALL, organomegaly
    - Died Day 10
  - 1 cerebral hemorrhage
    - B2202-1401-009
    - 6 year-old boy
    - (b) (6) infusion with tisagenlecleucel
    - CRS on Day 4, Grade 4 with ventilation, high-dose pressors, disseminated intravascular coagulation. Treated with tocilizumab, corticosteroids, and siltuximab. Dialysis started on Day 12.
    - Day 15 fatal cerebral hemorrhage

- 9 after 30 days
  - 6 from ALL
  - 1 encephalitis
    - B2202 -1100-002
    - 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 52 due to encephalitis; ALL in remission
  - 1 respiratory tract infection (bacterial)
    - B2202-1401-001
    - 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
    - B2202-1404-003
    - 18 year-old white 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

5.2.4.8 Safety conclusions

Severe CRS (Grade 3 and 4) events were noted in 47% of subjects. These events are life-threatening and require supportive measures; 46% of all subjects required ICU admission, 25% of all treated subjects required high-dose vasopressor support, 15 % required mechanical ventilation, 10% required dialysis for a mean duration of 11 days. One fatal outcome from severe CRS related coagulopathy resulted in death of a subject from cerebral hemorrhage. 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 15% of subjects 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 subjects, 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 subjects. Subjects 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.

Three subjects 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.

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.

6. RISK MITIGATION

The applicant proposed risk minimization activities to include a Risk Evaluation and Mitigation Strategy (REMS) in response to the risk of both cytokine release syndrome (CRS) and neurological toxicity. Their proposed REMS is a communication plan (via Dear Healthcare Provider Letters to pediatric oncologists and transplant specialists, REMS factsheet, CRS Management Algorithm, patient wallet card, and REMS website).

During the course of the Study B2202, site-selection and on-boarding were separate processes. The applicant has identified centers for initial launch, and developed training materials which include leukapheresis material collection, clinical overview, safety management, and others. The applicant selected sites which were previously accredited by the Foundation for the Accreditation of Cellular Therapy (FACT).

6.1 Pharmacovigilance and Long-Term Follow-up

The applicant has proposed two post-marketing studies to evaluate long-term safety, including an observational long-term follow-up study (referred to as "LTFU") for subjects who received tisagenlecleucel. These subjects who received tisagenlecleucel on the IND clinical trials will be followed according to protocol CCTL019A2205B.

Additionally, there is a prospective registry, protocol CTL019B2401, for patients treated with tisagenlecleucel after commercial availability (Table 10).

The applicant's pharmacovigilance plan (PVP) lists the following identified risks: cytokine release syndrome (CRS), neurologic/psychiatric events, tumor lysis syndrome, febrile neutropenia, infection, hematopoietic cytopenia, graft-vs-host disease, prolonged depletion of normal B cells, and hypersensitivity.

Additionally, the applicant lists the following as potential risks: secondary malignancy, new/exacerbated neurological event, new/exacerbated autoimmune disorder, new hematological disorder, vector virus replication. See CMC section for background information on the potential risks associated with this lentivirus transduced product.

Table 10. Applicant's Proposed Post-Marketing Registry (Protocol CTL019B2401)

Study title	Prospective registry to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel

Study design	Multicenter, prospective, observational, non-interventional, post-authorization safety study (PASS). Enrollment will be offered to pediatric, young adult and adult patients with B-cell malignancies who have received (or are due to receive) the product. Patients can enroll in this study on the day of or prior to the infusion, or within 3 months of receiving the infusion. This study will consist of a baseline period and follow-up period (up to 15 years post-infusion). A 5-year enrollment period is planned so the study duration will be approximately 20 years. All patients will be followed for survival.
Study population	Enrollment will be offered to every pediatric, young adult and adult B-cell malignancy patient who have received (or are due to receive) a product infusion for an approved indication as prescribed by their treating physician. Based on a recruitment projection with a drop-out rate of 15% over the 15-year follow-up phase, it is anticipated that approximately 4000 patients will be enrolled in the Registry over 5 years.
Primary Objectives/ Endpoints	The primary outcome variables are the type, frequency, and severity of adverse events (AE's) and laboratory abnormalities.
Secondary Objectives / Endpoints	• Describe the growth, development, and female reproductive status for patients who were aged < 18 years at the time of infusion. • Evaluate incidence and outcome of any pregnancy occurring in women of child-bearing potential after treatment with tisagenlecleucel
Data Analysis	• All AEs observed in this Registry will be summarized by frequencies and percentages by system organ class (SOC) using MedDRA and CTCAE version 4.03 and/or preferred term, severity (based on CTCAE grading or, the Penn grading scale for CRS for events of CRS), and type of AE. • Safety and effectiveness data will be summarized and listed by approved indication in an incremental manner and a cumulative manner. • Summaries of safety data pooled across indications will be reported periodically and at least annually, in accordance with regulatory requirements. • The final Clinical Study Report will be prepared, including all planned effectiveness and safety analyses at the end of the study after database lock. In addition, selected endpoints will be summarized by pediatric and adult age groups.

Study Time-Line	• Start of data collection: Upon commercialization • End of data collection: 20 years after start of data collection • Safety reports will be submitted periodically in accordance with local regulatory requirements for the duration of the study. • Registration in the EU PAS register: Not registered

7. DRAFT POINTS FOR THE ADVISORY COMMITTEE TO CONSIDER:

Chemistry, Manufacturing, and Controls

Draft Discussion Point 1:

Control of product quality for tisagenlecleucel is demonstrated by the design of the CAR structure and viral vector, manufacturing controls, and product testing. Each lot (batch) of product is tested before release for administration to ensure it meets specifications for defined product quality attributes. During development, the applicant established product quality specifications to assess CAR expression and T cell activity, including transduction efficiency by flow cytometry, vector copy number per cell, and the IFN-γ production upon stimulation of the final cell product with a CD19+ antigen presenting cell line.

Please discuss the following aspects of the control of product quality of tisagenlecleucel:

1. The design of the CAR construct and viral vector.
2. The assessment of CAR expression and T cell activity through
    a. The number of transduced T cells
    b. The number of vector copies per cell
    c. Antigen-specific T cell function (e.g., IFN-γ production and cytotoxicity upon stimulation)

Please comment on any other measurements, such as T cell subpopulations (cell surface marker characterization), that could provide greater assurance of product safety or efficacy.

Draft Discussion Point 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 genotoxicity.
c) Please discuss the impact of product testing on mitigation of risk for RCR and insertional mutagenesis.

Safety

Background:
Study B2202 was a prospective study of tisagenlecleucel, an anti-CD19 CAR T cell product for patients with relapsed or refractory ALL.

Life-threatening Cytokine Release Syndrome (Grade 3 and 4 CRS) events were noted in subjects who received tisagenlecleucel. The applicant's treatment algorithm requires risk mitigation measures (for example, availability of tocilizumab prior to tisagenlecleucel infusion at the treatment site) and close monitoring to permit early intervention and extensive supportive care measures to manage any resultant multi-organ dysfunction and coagulopathy.

Tisagenlecleucel was also associated with transient but ≥ Grade 3 neurotoxicity (including encephalopathy, seizures). Other serious and severe adverse events included infectious complications and resulting deaths, prolonged cytopenias, hypogammaglobulinemia, and coagulopathies.

In Study B2202, training of physicians and health care providers were required. In addition pre-infusion requirements included specific safety measures in place. The benefit-risk assessment and conclusions of effectiveness from Study B2202 were made in the setting of stringent risk-mitigation strategies.

Draft Discussion Point 3:

If tisagenlecleucel is approved by the FDA, please discuss which, if any, of the following would be necessary to ensure safe use of tisagenlecleucel in patients.

a) A Warning in the Prescribing Information that describes the risk of CRS and other adverse events of special interest.

b) Detailed instructions in the Prescribing Information for management of CRS, neurotoxicity, and Adverse Events of Special Interest.

c) Information about the risks and management of CRS distributed to oncology healthcare providers (e.g., physicians, nurses, nurse practitioners, physician's assistants).

d) Product-specific training and certification for individual prescribers and healthcare facilities to educate on the management of the acute toxicities of cytokine release syndrome and neurotoxicity.

e) Restricted distribution to hospitals that have documented training for hospital-based healthcare providers (e.g., staff nurses).

f) Measures to assure that tocilizumab will be on site, and that have written procedures in place for management of patients who will receive tisagenlecleucel.

g) Real-time monitoring for, and detailed evaluation of, every case of Grade 4 CRS or any fatal events that occur within 30 days after tisagenlecleucel infusion, to facilitate revision of the risk mitigation strategy.

Please discuss each element above, along with any other measures that you recommend to assure safe use of tisagenlecleucel.

Draft Discussion Point 4:

LTFU discussion:

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

Please discuss the follow-up that you would recommend for patients who receive tisagenlecleucel post-marketing.

- Please discuss the possible use of a patient registry to maintain contact with the patients for 15 years.
- Please discuss the recommended follow-up for persistence of the transduced tisagenlecleucel cells. This should include a discussion of the frequency, duration, and type (e.g., passive or active, with blood samples stored for future evaluation if malignancy occurs) of follow-up.

Benefit/Risk

Background:

Key efficacy results are shown below:

- CR+CRi 52
  - Infused Population 52/63 (82.5%)
- MRD-Negative CR/CRi Day 28;
  - 52 CR + CRi 52/52 (100%)
- Duration of Response (DOR: Among the 52 responders, the median DOR was not yet reached, with the median follow-up of 4.8 months and a maximum follow-up of 14.1 months(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).

However, tisagenlecleucel has also been associated with life-threatening adverse events including CRS and neurotoxicity.

Draft Discussion Point 5:

Based on the efficacy and safety results of Study B2202, please discuss whether the benefits justify the risks of tisagenlecleucel for treatment of pediatric and young adult patients (age 3-25) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell acute lymphoblastic leukemia (ALL).

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9. APPENDICES

APPENDIX 1

Response Definitions

Table 11 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 10e9/L, and • Platelets > 100 x 10e9/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, except that the following exist: • Neutrophils ≤ 1 x 10e9/L, and/or • Platelets ≤ 100 x 10e9/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: National Comprehensive Cancer Network (NCCN) guidelines for response

APPENDIX 2
CRS Grading and Management of CRS and Infusion Reactions

Table 12 Tisagenlecleucel-therapy associated Grading for CRS: Penn Grading Scale

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	Life-threatening complications such as hypotension requiring high-dose pressors or hypoxia requiring mechanical ventilation

The Penn Grading Scale for CRS			
1	**2**	**3**	**4**
		suspected infection due to fevers and/or neutropenia may have grade 2 CRS	
• 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

Table 13. 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.	

Table 14. 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

CRS Treatment Algorithm
• 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)

APPENDIX 3

Table 15 Summary of Adverse Events (B2202) with 20% cut-off All Grades; Post-Infusion of tisagenlecleucel

Adverse Event	Tisagenlecleucel n (%) n=68
Cytokine release syndrome	53 (77.94%)
Fever	27 (39.71%)
Febrile neutropenia	25 (36.76%)
Decreased appetite	25 (36.76%)
Headache	24 (35.29%)
Hypotension	21 (30.88%)
Anemia	21 (30.88%)
Hypogammaglobulinemia	20 (29.41%)
Neutrophil count decreased	20 (29.41%)
White blood cell count decreased	20 (29.41%)
Aspartate aminotransferase increased	19 (27.94%)
Vomiting	18 (26.47%)
Diarrhea	18 (26.47%)
Alanine aminotransferase increased	18 (26.47%)
Platelet count decreased	18 (26.47%)
Nausea	18 (26.47%)
Hypophosphatemia	17 (25.00%)
Tachycardia	17 (25.00%)
Hypocalcaemia	16 (23.53%)
Hypoxia	16 (23.53%)
Hypokalemia	16 (23.53%)
Lymphocyte count decreased	15 (22.06%)
Fatigue	15 (22.06%)

Source: JReview assessment of AEs

APPENDIX 4

Table 16. Serious Adverse Events ≥ 2% in Subjects post-infusion with tisagenlecleucel

Treatment-Emergent Serious Adverse Events	tisagenlecleucel n*=68 (%)
Cytokine release syndrome	43 (63.24%)
Febrile neutropenia	14 (20.59%)
Hypotension	8 (11.76%)
Acute kidney injury	5 (7.35%)
Fever	5 (7.35%)
Hypoxia	4 (5.88%)
Upper respiratory tract infection	3 (4.41%)
Respiratory failure	3 (4.41%)
Cardiac arrest	3 (4.41%)
Respiratory distress	2 (2.94%)
Pleural effusion	2 (2.94%)
Back pain	2 (2.94%)
Multiple organ dysfunction syndrome	2 (2.94%)
Mental status changes	2 (2.94%)
Aspartate aminotransferase increased	2 (2.94%)
Cardiac failure	2 (2.94%)
Respiratory syncytial virus infection	2 (2.94%)
Acute respiratory distress syndrome	2 (2.94%)
Tumor lysis syndrome	2 (2.94%)
Rhinovirus infection	2 (2.94%)
Disseminated intravascular coagulation	2 (2.94%)
Pancreatitis	2 (2.94%)

*subjects [Source: JReview SAE]