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Biologics License Application (BLA) Clinical Review and Evaluation

Application Type	Efficacy Supplement BLA
Application Number(s)	125646/663
Priority or Standard	Priority
Submit Date(s)	27 August 2021
Received Date(s)	27 August 2021
PDUFA Goal Date	28 May 2022
Division/Office/Center	DCEPT/OTAT/CBER
Review Completion Date	26 May 2022
Established Name	Tisagenlecleucel
(Proposed) Trade Name	KYMRIAH
Pharmacologic Class	CD19-directed, genetically modified autologous T cell immunotherapy
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	Cryopreserved injection containing 31.25% (v/v) of Plasma-Lyte A, 31.25% (v/v) of 5% Dextrose/0.45% sodium chloride, 10% Dextran 40 (LMD)/5% Dextrose, 20% (v/v) of 25% Human Serum Albumin (HSA), and 7.5% (v/v) Cryoserv® dimethylsulfoxide (DMSO), and supplied in one to three patient specific infusion bags
Dosing Regimen	A single dose with a target of 0.6 to 6.0 x 10^8 CAR-positive viable T cells, administered by intravenous infusion, and preceded by conditioning chemotherapy
Applicant Proposed Indication(s)/Population(s)	Adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s)	Adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy

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OBPV Reviewer	Kerry Welsh
BIMO reviewer	Triet Tran
APLB	Dana Jones

OCE=Oncology Center of Excellence
CHB=Clinical Hematology Branch
DCEPT=Division of Clinical Evaluation and Pharmacology/Toxicology

Glossary

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
BLA	Biologics License Application
BMI	body mass index
BOR	best overall response
CAR-T	chimeric antigen receptor T-cell
CI	confidence interval
CKAS	Cellular kinetic analysis set
CNS	central nervous system
CR	complete response
CRR	complete response rate
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EAS	Efficacy Analysis Set
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FU	follow-up
GELF	Groupe d'Etude des Lymphomes Folliculaires
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
IRC	Independent Review Committee
IV	intravenous
LD	lymphodepleting
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mEAS	modified Efficacy Analysis Set
MZL	marginal zone lymphoma
NALT	new anti-lymphoma therapy
NE	not estimable
NHL	non-Hodgkin lymphoma
NR	not reached
OOS	out-of-specification

ORR	overall response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
POD24	progression of disease within 24 months from anti-CD20 containing first-line therapy
PPS	Per-protocol set
PR	partial response
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QoL	quality of life
r/r	relapsed or refractory
RCL	replication competent lentivirus
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SD	standard deviation
SITC	Society for Immunotherapy of Cancer
SNAR	serious neurological adverse reactions
SOC	standard of care
TEAE	Treatment emergent adverse event
TMTV	total metabolic tumor volume
TPAS	Tocilizumab pharmacokinetic analysis set
UK	United Kingdom
USA	United States of America
USPI	US prescribing information
WBC	white blood cell

1 Executive Summary

1.1. Product Introduction

The FDA's Assessment:

KYMRIAH (hereafter referred to as tisagenlecleucel) is an autologous anti-CD19 chimeric antigen receptor T cell (CAR-T cell) therapy engineered ex vivo to target CD19 on the surface of B lymphocytes. The applicant's proposed new indication is for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy. The review team recommends accelerated approval of tisagenlecleucel for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy. Tisagenlecleucel is currently approved for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (B-ALL) refractory or in second or later relapse, as well as in adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. The recommended dose for the proposed FL indication is a single intravenous infusion of 0.6 to 6.0 x 10^8 CAR-positive viable T cells following lymphodepletion with either fludarabine and cyclophosphamide or with bendamustine.

In support of this application, the applicant submitted safety and efficacy data from the clinical study, ELARA (also known as CCTL019E2202, hereafter referred to as 'E2202' Study). E2202 is a single-arm phase 2 multicenter, multinational trial that enrolled patients ≥18 years of age with r/r FL grade 1, 2 or 3A, who were either refractory to a second or later line of therapy (including anti-CD20 antibodies and alkylating agents) or relapsed within 6 months after completion of second or later line of systemic therapy, during anti-CD20 antibody maintenance (following at least two prior lines of therapy) or within 6 months after maintenance therapy or relapsed after autologous hematopoietic stem cell transplant (HSCT). Patients were excluded if they had evidence of histologic transformation, FL grade 3B, previous anti-CD19 CAR-T cell therapy or allogenic HSCT. In total, 98 subjects were enrolled (i.e., underwent leukapheresis), and 97 subjects were treated with tisagenlecleucel. One subject did not receive tisagenlecleucel since the subject achieved complete response to previous anticancer therapy. These 97 subjects constituted the safety analysis set. The first 90 consecutively enrolled subjects, as specified in the protocol, who had measurable disease at baseline per independent review committee (IRC) and had a minimum of 9 months follow-up from the first response to the data cutoff date of 29 March 2021 or discontinued earlier, were included in the primary efficacy analysis.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA's Assessment:

E2202 provided substantial evidence of efficacy of tisagenlecleucel in the intended r/r FL population, based on overall response rate and duration of response and supported by complete response rate. Among 90 subjects included in the primary efficacy analysis, the median number of prior therapies was 4 (range: 2 to 13). Eighty-seven percent had Stage III-IV disease at study entry, 64% had bulky disease, 36% had a prior autologous HSCT, and 66% had progression within 24 months of initiating their first anti-CD20 combination therapy (POD24). Between leukapheresis and administration of tisagenlecleucel, 44 patients (49%) received bridging chemotherapy. The subjects were treated with a single dose intravenous infusion of tisagenlecleucel with a target dose of 0.6 to 6.0 × 10^8 CAR-positive viable T cells. The median dose administered was 2.06 × 10^8 CAR-positive viable T-cells (range: 0.1 to 6.0 × 10^8 CAR-positive viable T cells). The disease response was determined by an Independent Review Committee (IRC) per the Lugano Response Criteria (Cheson et al 2014) and adjudicated by the FDA.

Efficacy:

The primary efficacy analysis was performed in a prospectively identified cohort of 90 subjects as defined above as the 'Primary Efficacy Population'. The ORR was 85.6% (95% confidence interval [CI]: 76.6, 92.1) with a CR rate of 67.8% (95% CI: 57.1, 77.2). With an estimated median follow-up from date of first response of 9.1 months, the median DOR was not estimable (NE) (95% CI: 15.6 months, NE), and the 1-year rate of continued remission was 70.8% (95% CI: 58.0, 80.3). On intention-to-treat (ITT) analysis, of the 98 subjects with r/r FL who underwent leukapheresis, the ORR was similar at 86% with a CR rate of 67%.

The ORR of 86% seen in Study E2202 compares favorably to ORRs noted with available therapies with regular approval, which ranges from 59% to 80%. Furthermore, the ORR also compares similarly with available therapies with accelerated approval, which range from 34% to 91%. The CR rate of tisagenlecleucel in this patient population also compares favorably with available therapies. Although the median DOR seen with tisagenlecleucel was not reached, there is not enough information to assess the longer-term durability of the treatment effect with tisagenlecleucel in subjects with r/r FL, in comparison to that observed with currently available therapies with regular approval. The magnitude of the treatment effect was consistent across other exploratory subgroup analyses of both ORR and CRR in relation to key disease or treatment characteristics.

Considering the life-threatening nature of r/r FL and the therapies available to this population, the clinical review team assesses a favorable benefit-risk profile and has determined that tisagenlecleucel provides an meaningful therapeutic advantage based

on objective response rate, further supported by durability of response, in the context of currently available therapies for patients with r/r FL. The clinical review team thus recommends accelerated approval of tisagenlecleucel for the treatment of adult patients with r/r FL after two or more lines of systemic therapy.

Accelerated approval may be considered for an agent that addresses an unmet medical need based on an appropriate surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit. The ORR observed in the E2202 Study, supported by the durability of response, serves as an intermediate clinical endpoint reasonably likely to predict clinical benefit in this difficult to treat patient population. For products granted accelerated approval, a postmarketing confirmatory trial is generally required to verify clinical benefit. The applicant plans to conduct a phase 3 randomized control trial with the primary endpoint of progression-free survival, as a postmarketing requirement (PMR) study, to verify the clinical benefit of tisagenlecleucel in adult patients with r/r FL.

Safety:

The E2202 study was the primary source for safety data and included a total of 97 subjects with r/r/ FL who were treated with tisagenlecleucel. Grade 3 or higher adverse reactions occurred in 76 (78.4%) subjects. Sixty-nine (71%) subjects developed grade 3 or higher adverse reactions within 8 weeks of tisagenlecleucel infusion. Adverse events of special interest included: cytokine release syndrome (CRS) (53%) with no grade ≥ 3 CRS; neurologic toxicities (43%) with grade ≥ 3 in 6%; prolonged cytopenia (grade ≥ 3 thrombocytopenia in 17% and grade ≥ 3 neutropenia in 16%); infections in 52% with ≥ grade 3 infections in 21%, including a fatal infection in one subject; and hypogammaglobulinemia in 17%.

During the conduct of E2202 Study, the risk of life-threatening and fatal adverse reactions attributed to tisagenlecleucel was mitigated by mandated site and investigator training, careful site selection and monitoring, and instructions for early detection and management of the most serious complications. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and neurologic toxicities, and a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU). The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies with emphasis on early recognition and treatment of CRS and neurologic toxicities. To alert prescribers to clinically significant, serious, life-threating, and fatal adverse reactions associated with tisagenlecleucel, the following events will be included in the Warning and Precautions section of the label: CRS, neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), serious infections, prolonged cytopenias, hypogammaglobulinemia, and secondary malignancies.

The theoretical concerns include an increased risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional mutagenesis. There were no events of RCR infection or insertional mutagenesis reported in this sBLA.

Long-term safety after treatment with tisagenlecleucel, particularly from the risk of insertional mutagenesis related secondary malignancies, remains a concern due to the limited follow-up duration. Therefore, a PMR long-term follow-up (LTFU) registry study for follow-up up to 15 years is warranted.

In summary, E2202 Study is a single-arm study which provides substantial evidence of efficacy, based on overall response rate, further supported by durability of response, in adult subjects with r/r FL after two or more lines of systemic therapy, with an acceptable safety profile. Given the life-threatening nature of the disease with significant unmet need, the adverse reactions of CRS, neurologic toxicities and HLH/MAS, if managed appropriately, represents toxicities that are acceptable from a benefit-risk perspective in the intended population. Thus, the overall benefit-risk profile of tisagenlecleucel in adult patients with r/r FL after at least two lines of systemic therapy is favorable and supports accelerated approval. Continued approval for this indication will be contingent upon verification of clinical benefit in confirmatory trial(s).

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The FDA's assessment:

The table below summarizes the benefit-risk considerations for tisagenlecleucel for the treatment of adult patients with relapsed or refractory FL. In summary, the overall results of a high overall response rate with durability of response in adult patients with r/r FL after two or more prior lines of systemic therapies, supports substantial evidence of effectiveness of tisagenlecleucel.
The safety profile of tisagenlecleucel in treatment of adults with r/r FL appears similar to the safety profile in the other approved indications. CRS or NT can be life-threatening or fatal and requires institution of Risk Evaluation and Mitigation Strategies (REMS). Some patients may develop HLH/MAS, which could result in a fatal outcome. Hypogammaglobulinemia may predispose patients to serious infection and require monitoring and intervention. Prolonged cytopenias may again increase the risk of serious infections and require long term transfusions or growth factor support. However, these risks may be managed with appropriate monitoring and mitigation strategies in place. Therefore, these adverse events represent toxicities that are acceptable from a benefit-risk perspective in the intended population. Thus, the overall benefit-risk prolife of tisagenlecleucel in adult patients with r/r FL after at least two lines of systemic therapy is favorable and supports accelerated approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• FL is an indolent NHL, characterized by high risk of relapse. Chance of response and the prognosis worsens with subsequent relapses. • Median progression-free survival (PFS) decreases from 6.6 years in association with first line of therapy to 1.5 and 0.83 years with second- and third-line therapies, respectively (Link et al 2019). • Cumulative toxicities from multiple therapies and resistance or transformation to high-grade or aggressive lymphomas eventually lead to death.	• r/r FL is a serious and fatal disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current treatment approach includes chemo-immunotherapy, high dose chemotherapy followed by autologous SCT, allogenic SCT in selected cases, PI3K inhibitors, EZH2 inhibitors or CD19 CAR T cell therapy. • Although the ORR with currently approved drugs ranges from 34 to 91%, durability of response remains limited. • Relapses following above therapies are challenging to treat.	• The available treatment options for patients with r/r FL remains limited. • Many patients still relapse after these therapies making patients less responsive to subsequent lines of therapies. • There is need for more innovative therapies with high and durable response rates.
Benefit	• Study E2202 was a single-arm multicenter international study which enrolled adult patients with r/r FL after ≥ 2 lines of systemic therapy. • Subjects received single infusion of tisagenlecleucel following lymphodepletion. • The primary endpoint was Complete Response rate (CR rate) • In the efficacy analysis set (N=90), the CR rate was 68%, and the overall response rate was 86%. • With the median follow up of 9.1 months from first response, the median duration of response was not estimable (95% CI 15.6, NE). • The median time to first response was 2.9 months (range 0.6 to 6.0 months)	• The high overall response rate, supported by CRR, with durability of response, provides robust evidence of clinical benefit.
Risk and Risk Management	• The serious adverse events were CRS, NT, HLH/MAS, prolonged cytopenia, hypogammaglobulinemia and serious infections. • CRS and NT were mitigated by requirement of REMS, careful site selection and training of investigators. • There is theoretical risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional	• The evidence suggests that the risk of tisagenlecleucel, while substantial, does not outweigh the clinical benefit in adult patients with r/r FL. • The risks associated with tisagenlecleucel warrants a boxed warning, a REMS with ETASU, and a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mutagenesis. However, no such cases occurred by the data cutoff date in this study.	long term follow up study.

1.4. Patient Experience Data

The FDA's Assessment:

The applicant submitted patient reported outcomes (PROs) collected using three different instruments (FACT-LYM/SF-36 questionnaires, EQ-5D-3L Questionnaire and EQ-VAS Score). However, because the study was a single arm study with no comparator, the PRO data is descriptive and is not considered for inclusion in labeling.

Table 1: Applicant/FDA - Patient Reported Outcomes (PROs)

Check if submitted	Type of Data	Section Where discussed, if Applicable
☒	Patient-reported outcome	Section 8.1
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if considered	**Type of Data**	**Section Where discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's position

Epidemiology and disease background

Follicular lymphoma (FL) is the second most common lymphoma diagnosed in the United States and Western Europe, accounting for approximately 35% of all non-Hodgkin lymphomas (NHL), and 70% of indolent lymphomas (Freedman and Jacobsen 2020). In the US, there were 74,200 cases of NHL (12688 cases of FL) in 2019, with approximately 19,970 disease-specific related deaths overall. The estimated incidence in 2020 (77,240 cases) shows a 4.4% increase over 2019 (SEER 2019, SEER 2020).

Most patients are diagnosed with advanced disease during the sixth decade of their life, but approximately 25% of patients are ≤ 40 years of age (Jaglowski et al 2009). Immune suppression or auto-immune diseases, exposure to herbicides and pesticides, and use of hair spray have been linked to the development of FL. The incidence is higher in industrialized countries than in developing countries, and higher in men than in women (Carbone et al 2019, Dada 2019).

FL is derived from the germinal center and characterized by well-preserved follicles, where malignant cells typically co-express CD10 (89% of cases), CD19 (50% to 79% of cases), CD20, and B-cell leukemia/lymphoma 2 protein (BCL2; 85% of cases) (Gaulard et al 1992, Almasri 1998). Genetic alterations cause dysregulation of epigenetic modifiers, clonal expansion, and additional genomic modifications resulting in FL development. FL is classified histologically into three grades based on the number of centroblasts (Swerdlow et al 2008).

Most patients with FL have widespread disease at diagnosis, including lymph nodes, spleen, and bone marrow involvement.

Several measures of outcome for patients with FL have been developed. The Follicular Lymphoma International Prognostic Index (FLIPI) score incorporates five clinical factors (age, stage, serum hemoglobin level, number of nodes involved, and LDH level) to identify risk groups with significantly different survival outcomes (Brice et al 1997, Solal-Céligny et al 2004); this was initially developed in the pre-rituximab era but has demonstrated its prognostic value also in rituximab-treated populations (Nooka et al 2013). A study in patients with previously untreated FL treated with R-CHOP chemotherapy (rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone), showed that including the mutational status of 7 genes along with the FLIPI score (called the m7 FLIPI), led to better prognostication of 5-year failure-free survival (Pastore et al 2015). The GELF criteria (Brice et al 1997), which include parameters of tumor burden and clinical findings, present another model for risk stratification. Analysis of the prospective PRIMA trial has led to a simple new prognostic model based upon bone marrow involvement and β2-microglobulin for PFS called PRIMA-PI (Bachy et al 2018).

At the time of relapse, the best predictor of tumor aggressiveness is the duration of remission following initial treatment.

Histologic transformation of FL from an indolent disease to more aggressive

lymphomas, mainly diffuse large B-cell lymphoma (DLBCL), occurs in 10% to 70% of patients over time, at a rate of 2% to 3% per year, and is associated with rapid progression of lymphadenopathy, extranodal disease (besides the marrow), B symptoms, hypercalcemia, and elevated serum LDH (Freedman 2018).

Relapsed/refractory FL

FL follows a clinical course characterized by numerous periods of remission that alternate with relapses, with treatment efficacy and duration of remission declining with each successive therapy. FL is considered incurable, and death generally occurs due to histological transformation to DLBCL or because FL becomes refractory to chemotherapy (Carbone et al 2019).

Approximately 20% of patients with FL experience progression of disease within 2 years of initial chemo-immunotherapy (POD24) (Rummel et al 2013), and this subset of patients has a particularly poor prognosis, with a median 5-year survival of 50%, compared to 90% in patients without POD24 (Casulo et al 2015).

Moreover, patients with relapsed or refractory (r/r) FL will experience progressively shorter responses to subsequent treatments (second- or later lines of therapy). In a retrospective multicenter study of 348 patients with FL requiring first-line therapy, 111 patients, 41 patients, and 15 patients received second-, third-, and fourth-line therapies, respectively. Median survival after first- line therapy was not reached, after second-line therapy it was 7.6 years, and after third-line therapies 4.8 years; the 10-year survival rate was only 20% after third-line treatment (Rivas-Delgado et al 2019).

Median progression-free survival (PFS) decreases from 6.6 years in association with first line of therapy to 1.5 and 0.83 years with second- and third-line therapies, respectively (Link et al 2019).

The development of anthracycline-containing chemotherapy and use of anti-CD20 monoclonal antibodies (including rituximab) have improved outcomes for FL (Tan et al 2013).

Cumulative toxicities from multiple therapies and resistance or transformation to high-grade or aggressive lymphomas are also major challenges in this population. Histological transformation to aggressive lymphomas is associated with poor outcome, with a median overall survival (OS) of 50 months after transformation. Survival is lower in patients who experience transformation early (< 18 months) versus late (≥ 18 months) after FL diagnosis (5-year OS: 22% vs. 76%) (Link et al 2019). In a pooled analysis of US and French cohorts, histological transformation was the leading cause of death (77 of 140 deaths) in patients with newly diagnosed FL (Sarkozy et al 2019).

These observations emphasize the need for novel, improved therapies for r/r FL.

The FDA's Assessment:

Follicular lymphoma (FL), comprising roughly 35% of non-Hodgkin lymphomas (NHLs), is an indolent but rarely curable malignancy arising from B cells found in the germinal center of lymph nodes. As a B cell disorder, FL expresses the surface antigens CD19 and CD20, among others. The disease is further characterized by an overexpression of the apoptosis regulator B-cell lymphoma 2 (BCL-2), driven by the t (14;18) translocation found in 85% of cases. The annual incidence of FL is about 2.5 – 3 cases per 100,000 Americans, predominantly Caucasians and with nearly equal incidence in men and women. Median age at diagnosis is 65 years. Although 40 – 80% of patients achieve a complete response to frontline chemoimmunotherapy, relapse over time is nearly universal, and prognosis progressively worsens with each recurrence. It is established that patients having relapse after autologous stem cell transplantation and progression of disease within 24 months of initial chemoimmunotherapy (POD24) have an inferior prognosis, including shorter overall survival. Additionally, transformation to the aggressive disease diffuse large B-cell lymphoma (DLBCL) is a well-described phenomenon, which eventually leads to death.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Currently, the management of relapsed FL is generally predicated on the use of non-cross-resistant agents. The choice of treatment after the initial relapse depends on the type of previous therapy, response, and duration of response (DOR). Therefore, selecting therapies for patients with FL remains an empiric exercise that includes patient choice and the aim to balance improved disease-free survival with maintenance of a good quality of life.

Patients who have been heavily pretreated such as those receiving 2 or more prior lines of therapy (including currently approved treatment) or failing autologous hematopoietic stem cell transplant (HSCT), and in particular those who are early relapsing, double refractory, or refractory to the preceding line of therapy, have limited treatment options (see Table 2). Though most available treatments have partially improved the prognosis of r/r FL, there are still major limitations associated with their use marked by recurrent relapses and progressively shorter duration of responses. With the exception of CAR-T-based therapies, other available treatment options have the following disadvantages:

- Poor complete response (CR) rates and DOR. In FL, achieving a CR is associated to increased DOR and potentially survival (Shi et al 2017). Disappointingly, CRs are in the order of 1-39% with currently approved therapies. Need for several cycles or chronic treatment, often with multiple agents, and long-term side effects of chronic treatments can lead to dose reductions or, in up to 20% of cases, dose interruptions and can significantly impact on quality of life (QoL).

- Do not offer the potential for cure. The only available potentially curative option for refractory patients is allogeneic HSCT; however, it can be offered only to highly selected patients and the associated mortality is high (24%).

Table 2: Applicant – Summary of therapies for r/r FL, per current USPIs

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Rituxan (rituximab)	Treatment of adult patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent	1997 Full approval	375 mg/m^2 as an IV infusion once weekly for 4 or 8 doses	ORR: 36% - 57% CRR: 3% - 14% Median DOR: 6.9 months – 15.0 months	Warnings and Precautions per prescribing information: Infusion-related reactions, severe mucocutaneous reactions, hepatitis B reactivation, PML, tumor lysis syndrome, infections, cardiovascular adverse reactions, renal toxicity, bowel obstruction and perforation, immunization, embryo-fetal toxicity.
Zevalin (ibritumomab tiuxetan)	Treatment of adult patients with relapsed or refractory, low-grade or follicular B-cell NHL	2002 Full approval	Day 1: IV infusion of 250 mg/m^2 of rituximab Day 7, 8, or 9: IV infusion of 250 mg/m^2 of rituximab; within 4 hours, IV infusion of Zevalin over 10 minutes as follows: 0.4 mCi/kg (14.8 MBq/kg) for patients with normal platelet count or 0.3 mCi/kg (11.1 MBq/kg) in r/r patients with platelet count of 100,000 – 149,000 cells/mm^3	ORR: 74% - 83% CRR: 15% - 38% Median DOR: 6.4 months – 14.3 months	Warnings and Precautions per prescribing information: Serious infusion reactions, prolonged and severe cytopenias, severe cutaneous and mucocutaneous reactions, risk of developing myelodysplastic syndrome, leukemia, and other malignancies, extravasation, risks of immunization, radionuclide precautions, embryo-fetal toxicity.

Treanda (bendamustine)	Treatment of patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen	2008 Full approval	120 mg/m^2 administered IV over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles	ORR: 74% CRR: 13%	Warnings and Precautions per prescribing information: Myelosuppression, infections, PML, anaphylaxis and infusion reactions, tumor lysis syndrome, skin reactions, hepatotoxicity, other malignancies, extravasation injury, embryo-fetal toxicity.
Gazyva (obinutuzumab)	Treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen, in combination with bendamustine followed by GAZYVA monotherapy	2017 Full approval	1000 mg IV on Days 1, 8, and 15 of Cycle 1, then 1000 mg on Day 1 of Cycles 2-6 or Cycles 2-8, then 1000 mg monotherapy every two years months for up to two years	ORR: 79% CRR: 16% Median DOR: NR Median PFS: NR vs 13.8 months for bendamustine (HR=0.48 [0.34, 0.68]) <u>Subanalysis of patients with >2 prior therapies</u> ORR: 75%, CRR: 20%, Median DOR: NR vs 79%, 20%, and 13 months for bendamustine, respectively (FDA 2021)	Warnings and Precautions per prescribing information: Hepatitis B virus reactivation, PML, infusion-related reactions, hypersensitivity including serum sickness, tumor lysis syndrome, infections, neutropenia, thrombocytopenia, immunization, embryo-fetal toxicity.
Revlimid (lenalidomide)	Treatment of adult patients with previously treated FL in combination with a rituximab product	2019 Full approval	20 mg orally once daily on Days 1-21 of repeated 28-day cycles for up to 12 cycles of treatment in combination with a rituximab-product	<u>AUGMENT trial</u> Median PFS (FL+MZL): 39.4 months vs 14.1 months for rituximab (HR=0.46 [0.34, 0.62]) ORR: 78% vs 53% for rituximab <u>Subanalysis of patients with >2 prior therapies</u> ORR: 81%, CRR: 34%, Median DOR: NR (FDA 2021)	Warnings and Precautions per prescribing information: Embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism, second primary malignancies, hepatotoxicity, severe cutaneous reactions, tumor lysis syndrome, tumor flare reaction, impaired stem cell mobilization, thyroid disorders, hypersensitivity.
Zydelig (idelalisib)	Treatment of patients with relapsed follicular B-cell NHL	2014 Accelerate	150 mg administered orally	ORR: 54% CRR: 8%	Warnings and Precautions per prescribing information:

	(FL) who have received at least two prior systemic therapies	d approval	twice daily with or without food	Median DOR: NE	Hepatotoxicity, severe diarrhea or colitis, pneumonitis, infections, intestinal perforation, severe cutaneous reactions, hypersensitivity reactions, neutropenia, embryo-fetal toxicity.
Aliqopa (copanlisib)	Treatment of adult patients with relapsed FL who have received at least two prior systemic therapies	2017 Accelerated approval	60 mg administered as a 1-hour IV infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off).	ORR: 59% CRR: 14% Median DOR: 12.2 months	Warnings and Precautions per prescribing information: Infections, hyperglycemia, hypertension, non-infectious pneumonitis, neutropenia, severe cutaneous reactions, embryo-fetal toxicity.
Copiktra (duvelisib)	Treatment of adult patients with r/r FL after at least two prior systemic therapies	2018 Accelerated approval	25 mg administered orally twice daily with or without food	ORR: 42% CRR: 1%	Warnings and Precautions per prescribing information: Infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, neutropenia, embryo-fetal toxicity.
Tazverik (tazemetostat)	Treatment of adult patients with r/r FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies. Treatment of adult patients with r/r FL who have no satisfactory alternative treatment options	2020 Accelerated approval	800 mg orally twice daily with or without food	<u>EZH2 mutant FL</u> ORR: 69% CRR: 12% Median DOR: 10.9 months <u>EZH2 wild-type FL</u> ORR: 34% CRR: 4% Median DOR: 13.0 months	Warnings and Precautions per prescribing information: Secondary malignancies, embryo-fetal toxicity.
Ukoniq (umbralisib)	Treatment of adult patients with r/r FL who have received at least three prior lines of	2021 Accelerated approval	800 mg taken orally once daily with food	ORR: 43% CRR: 3% Median DOR: 11.1 months	Warnings and Precautions per prescribing information: Infections, neutropenia,

	systemic therapy				diarrhea or non-infectious colitis, hepatotoxicity, severe cutaneous reactions, allergic reactions due to inactive ingredient FD&C Yellow No. 5, embryo-fetal toxicity.
Yescarta (axicabtagene ciloleucel)	Treatment of adult patients with r/r FL after two or more lines of systemic therapy	2021 Accelerated approval	2×10^6 CAR-positive viable T cells per kg body weight	ORR: 91% CRR: 60% Median DOR: NE	Warnings and Precautions per prescribing information: Cytokine release syndrome, neurologic toxicities, hypersensitivity reactions, serious infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies, effects on ability to drive and use machines.
CRR: complete response rate; IV: intravenous; MZL: marginal zone lymphoma; NE: not estimable; NHL: non-Hodgkin lymphoma; NR: not reached; ORR: overall response rate; PML: progressive multifocal leukoencephalopathy; r/r: relapsed or refractory; USPI: US prescribing information					

The FDA's Assessment:

The treatment of relapsed refractory FL differs depending on prior therapies, length of remission, patient age, fitness and comorbidities, and physician/patient preferences. In general, National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines recommend following approach:

Table 3: FDA Reviewer – Current treatment approach for r/r Follicular Lymphoma

Treatment of r/r Follicular Lymphoma	
NCCN guidelines	ESMO guidelines
2nd Lines (Preferred regimens): Bendamustine, CHOP or CVP+rituxuimab or Obinutuzumab Lenalidomide+rituximab or Obinutuzumab Consolidation with ASTCT AlloHSCT (in selected cases) **3rd lines** PI3K inhibitors EZH2 inhibitor (Tazematostat) Anti CD19 CAR T cell therapies: axicabtagene ciloleucel	Chemoimmunotherapy, mainly Obinutuzumab or rituximab combined with bendamustine, CHOP or CVP. In selected cases: Rituximab monotherapy Radio-immunotherapy -Rituximab-lenalidomide -HDC followed by ASTCT -AlloSCT in selected cases

Three agents/treatment regimens currently have regular approval in the United States for the treatment of r/r FL: Lenalidomide+ rituximab or R^2 regimen, bendamustine and bendamustine+ Obinutuzumab. These regimens were approved based on the following key outcomes:

Table 4: FDA Reviewer – Summary of therapies for r/r Follicular Lymphoma which have FDA regular approval

Regimen	Indication/ Approval date	N	ORR	CRR	Median DOR (Months)
Lenalidomide+ Rituximab (R^2)	Previously treated FL; Approval date: 28 May 2019, based on following trials				
	AUGMENT	All=147	All=80% ≥2 prior=81	All=35% ≥2 prior=34%	All=36.6 (95% CI 24.9-NR) ≥2 prior=NR (95%

		≥2 prior=67	%		CI 19.6-NR)
	MAGNIFY	All: 177 ≥2 prior=115	All: 59% ≥2 prior=57%	All: 35% ≥2 prior=13%	All: NR with median F/U of 7.9 months ≥2 prior=5.1 (95% CI 2.8-8.5
Obinutuzumab + Bendmustine	FL relapsed after or refractory to a rituximab containing regimen Approval date: 26 February 2016	155	79%	16%	NR
Bendamustine	Indolent B-cell NHL progressed during or within six months of treatment with rituximab or a rituximab containing regimen Approval date: 31 October 2008	ALL: 100 FL: 62	74%	13% CR	9.2 (95% CI 7.1-10.8)
AUGMENT study exclude subjects refractory to rituximab, while the MAGNIFY study included these subjects. In MAGNIFY, 47% of the subjects who had received at least two prior lines of systemic therapy were refractory to rituximab. Source: USPI of each drug, FDA approval clinical review summaries, Published literature and Clinicaltrials.gov)					

Currently three drugs and one biologic agent (a CD19 CAR-T cell therapy) are available through accelerated approval for the treatment of r/r FL, as summarized below.
Two drugs with accelerated approval for r/r FL (duvelisib and idelalisib) have been voluntarily withdrawn for the FL indication. Additionally, the sponsor of umbralisib has announced to voluntarily withdraw its accelerated approval for FL indication.

Table 5: FDA Reviewer – Summary of therapies for r/r Follicular Lymphoma which have FDA accelerated approval

Drug	Indication/Approval date	N	ORR	CRR	Median DOR (Months)
Umbralisib	r/r FL after ≥3 prior	117	43%	3%	11.1 (95%

	lines of therapies (5 February 2021)				CI 8.3- 16.4) range (0.0- 20.9)
Tazemetostat	r/r with EZH2 mutation after ≥2 prior therapies or no satisfactory alternative treatment options (18 June 2020)	EZH2 mutant=42 EZH2 wt=53	EZH2 mutant= 69% EZH2 wt= 34%	EZH2 mutant= 12% EZH2 wt= 4%	EZH2 mutant=10.9 (95% CI 7.2- NE) Range (0+- 22.1+) EZH2 wt= 13.0 (95% CI 5.6- NE) Range (1- 22.5+)
Copansilib	relapsed FL after ≥2 prior lines of therapies (14 Sep 2017)	104	59%	14%	12.2 (range 0+ - 22.6)
Axicabtagene ciloleucel	Relapsed or refractory FL after ≥2 prior lines of therapies 5 March 2021	81	91%	60%	NE (95% CI 20.8, NE) range: 0.0, 25.0+
Source: USPI of each drug, FDA approval clinical review summaries, Published literature and Clinicaltrials.gov					

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

The original Biologics License Application (BLA 125646) for Kymriah (tisagenlecleucel) was approved on 30-Aug-2017 for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. A Risk Evaluation and Mitigation Strategy (REMS) was also approved with the BLA.

A supplemental BLA was approved on 01-May-2018 to add a new indication for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after

two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. A modification to the REMS was simultaneously approved to align with labeling changes related to the new indication.

The FDA's Assessment:

Tisagenlecleucel was the first CD19 CAR-T cell therapy approved by the FDA for treatment of patients from birth to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. Subsequently, it was approved for treatment of adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy including DLBCL NOS, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 6: Applicant – Overview of regulatory activities relevant for FL

Date	Event summary
20-Apr-2020	Regenerative Medicine Advanced Therapy designation granted for tisagenlecleucel for the treatment of refractory or relapsed follicular lymphoma
15-Sep-2020	Type B meeting to discuss the submission pathway for the sBLA
16-Sep-2020	Orphan-drug designation (#20-7651) granted for tisagenlecleucel for the treatment of follicular lymphoma
13-Apr-2021	Type B meeting to discuss the content and format of the planned sBLA
29-Jul-2021	Type B meeting to discuss the adequacy of the pivotal trial data to support submission of the sBLA; preliminary discussions were held regarding potential post approval requirement to conduct a clinical trial

The FDA's Assessment:

The study E2202 was conducted under IND 16130. The RMAT designation was granted for tisagenlecleucel for the treatment of relapsed/refractory follicular lymphoma on April 20, 2020. Subsequently, tisagenlecleucel was also granted orphan drug designation for the treatment of FL by the FDA on September 16, 2020 (# DRU-2020-7651). Please see below the key meetings that occurred prior to submission of this supplemental BLA application.

Table 7: FDA Reviewer – Regulatory meeting summary relevant to this supplemental BLA application

Date	Meeting Topic (Type)	Discussion	Format	FDA Meeting Minutes

September 15, 2020	Type B meeting	Post RMAT designation meeting to discuss further drug development	Teleconference	CRMTS#12705
April 13, 2021	Type B meeting	Discuss BLA submission	Written response	CRMTS#13194
July 29, 2021	Type B meeting	Discuss adequacy of data for sBLA submission	Teleconference	CRMTS#13474

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Compliance and Biologics Quality (OCBQ)

The FDA's Assessment:

There were no concerns/issues with regard to compliance or biologic quality.

4.2. Product Quality

The FDA's Assessment:

There were no CMC concerns regarding the product quality or manufacturing issues.

4.3. Devices and Companion Diagnostic Issues

The FDA's Assessment:

No additional device or companion diagnostic were needed to support the benefit risk assessment of this applicant.

5 Summary of Nonclinical Pharmacology/Toxicology Findings

No new information is provided in the current submission.

The FDA's Assessment:

There was no new preclinical or toxicology study results submitted along with this supplemental BLA application.

6 Clinical Pharmacology

Table 8: Applicant - Overview of key clinical pharmacology results of tisagenlecleucel in adult patients with r/r FL in Study CCTL019E2202

Key parameters	Results
Cellular kinetics	Similar geometric mean AUC0-84d and higher AUC0-28d and Cmax values in responders were observed compared to non-responders, which could be attributed to the high interindividual variability, small numbers of nonresponders, and overlapping expansion ranges observed between responders and nonresponders (Summary of Clinical Pharmacology-Table 3-1). The median Tmax in responders (9.92 days) was comparable to that in non-responders (13.0 days) (Summary of Clinical Pharmacology-Section 2).
Immunogenicity	No impact of anti-mCAR19 antibodies (humoral) and cellular immunogenicity on cellular kinetics and Month 3 response.
Intrinsic factors	
Age/race/body weight/gender	No impact of intrinsic factors on expansion and persistence.
Prior disease	No clinically relevant impact by disease stage at study entry, number of lines of therapy on expansion/persistence.
Pre-infusion tumor burden	Higher expansion in patients with high FLIPI relative to low or intermediate FLIPI.
CRS grade	Higher expansion (Cmax and AUC0-28d) observed in patients with any Grade CRS relative to patients with no CRS events. No Grade 3/4 CRS events noted within 8 weeks of infusion.
Extrinsic factors	
Prior therapy	No clinically relevant impact of prior HSCT status, prior bendamustine use, types of LD chemotherapy, number of lines of prior therapy on expansion. Only 5 patients received bendamustine as LD chemotherapy, and therefore a definitive conclusion cannot be made regarding the impact of type of LD chemotherapy (fludarabine + cyclophosphamide vs. bendamustine)
Concomitant therapy CRS management with tocilizumab	Higher AUC0-28d and Cmax observed in patients who received tocilizumab; however, this could be

Treatment with corticosteroid	confounded as patients with higher Grade CRS generally have greater expansion and these patients with high-Grade CRS require tocilizumab. Transgene continues to expand and persist following tocilizumab infusion. No difference in Tmax whether tocilizumab was administered or not (Summary of Clinical Pharmacology-Section 2.3.2). Three patients received corticosteroid for management of CRS, while all other patients received corticosteroid for reasons other than CRS; therefore, the impact of corticosteroid use on expansion cannot be studied.
Dose-efficacy	
Dose-response	No overall impact with slightly lower probability of response at the lower end of the dose range ($<1.0\times10^8$ cells). Favorable clinical responses (CR/PR) were observed across the entire recommended dose range.
Dose-DOR/Dose-time to response	No apparent impact of dose on DOR or PFS.
Dose-safety	
Dose-CRS	No apparent relationship. No severe cases of CRS (grade ≥3) observed within 8 weeks of infusion.
Dose-serious neurological events	No impact
Dose- time to resolution of hematopoietic cytopenias	No apparent impact
Exposure-efficacy	
Exposure-response	AUC0-28d and Cmax were higher in responding patients compared to non-responding patients (similar mean AUC0-84d estimates); however, this has to be interpreted with caution due to the large variability and the limited number of non-responding patients with evaluable Cmax.
Exposure-DOR	A longer DOR was associated with increasing exposure
Exposure-safety	
Exposure-CRS	Higher exposure metrics (AUC0-28d and Cmax) were associated with higher probability of any Grade CRS (Grade 1 or 2), however, CRS was manageable per CRS management algorithm. No Grade ≥ 3 cases of CRS were observed within 8 weeks of infusion.
Exposure-serious neurological events	No impact of exposure on neurological events.
Exposure-cytopenias	No apparent impact of exposure on time to resolution of cytopenias and serious neurologic events, despite the limited number of patients who experienced long term cytopenias.
Source: Summary of Clinical Pharmacology-Section 3, unless specified otherwise	

Responses were observed across the recommended dose range of 0.6 to 6.0×10^8 CAR-positive viable T cells. The key cellular kinetic conclusions are as follows (Summary of Clinical Pharmacology-Section 1.3):

- Long term persistence continued to be demonstrated in Study CCTL019E2202 for

up to a maximum of 558 days in responding patients and a maximum of 366 days in nonresponding patients.

- There was no apparent impact of dose on clinical response. Four patients received tisagenlecleucel products that were out-of-specifications (OOS) due to a lower dose than specified as per protocol (OOS range: 0.1 to 0.46 × 10^8 CAR-positive viable T cells), with no apparent impact on efficacy.
- No apparent impact of dose on clinical exposure was observed.
- Amongst the intrinsic factors evaluated (i.e., age, race, body weight, gender, prior disease, disease stage, burden of disease), none of these factors have clinically relevant impact on the cellular kinetics of tisagenlecleucel.
- Amongst the extrinsic factors (i.e., prior HSCT status and number of prior lines of therapy) studied, none of these factors have clinically relevant impact on the cellular kinetic properties of tisagenlecleucel. No definitive conclusion could be drawn regarding the impact of type of lymphodepleting (LD) chemotherapy (fludarabine + cyclophosphamide vs bendamustine) on exposure, as only 5 patients received bendamustine as LD chemotherapy
- Exposure-safety relationship: No Grade ≥ 3 CRS was observed in adult patients with r/r FL within 8 weeks of infusion. Higher exposure metrics (AUC0-28d and Cmax) were associated with incidence of any Grade CRS (Grade 1 or 2). Administration of tocilizumab was required for management of CRS in some patients; tisagenlecleucel transgene levels continue to expand and persist following tocilizumab administration. There was no apparent impact of exposure on time to resolution of cytopenias and serious neurologic events, despite the limited number of patients who experienced long term cytopenias.
- Dose-safety relationship: No apparent impact of dose on probability of CRS, all Grade serious neurologic events, or time to resolution of cytopenias was determined.
- Immunogenicity: Humoral and cellular immunogenicity results did not impact the cellular kinetics and BOR.

The FDA's Assessment:

Please see FDA Clinical Pharmacology reviewer's memo for discussion of this section.

Following are the summary of clinical pharmacology: (Source: FDA Clinical Pharmacology review memo)

The clinical pharmacology data was collected from Phase 2, single-arm, multicenter open label trial that evaluated the efficacy and safety of tisagenlecleucel in adult subjects with refractory or relapsed follicular lymphoma. The median age of the subjects in this clinical study was 57 years (range 29-73, N=97). The subjects were primarily White (75.3%) and 66.0% were male. The major clinical pharmacology findings are summarized in the following sections.

Pharmacokinetics (PK):

- The cellular kinetic profile of tisagenlecleucel is described by time course of transgene copies per microgram (µg) of DNA as measured by qPCR method. Summary statistics of PK parameters were based on the cellular kinetic analysis set (CKAS) (N = 94 subjects).
- The geometric mean area under curve from day zero to 84 (AUC0-84d) in responders (CR and PR) was comparable to that in non-responders (i.e., stable disease (SD) and progressive disease (PD)).
- The geometric mean AUC0-28d and maximum concentration (Cmax) values of responders was 186% and 109% higher compared to non-responders, respectively.
- The time to maximal expansion (Tmax) was comparable between the two groups (median Tmax:10 days and 13 days in responder and non-responder subjects, respectively).
- The persistence of the CAR-positive viable T cells was inferred based on Tlast value (time of last quantifiable concentrations) and half-life. The median Tlast value was 191 days (range 20-558) for responders versus 107 days (range19-336). The geometric mean half-life for responder subjects was 44 days (range 3-601 days) and half-life was 24 days (range 3-103 days) in non-responders.
- Intrinsic factors such as age, race and gender have no impact on cellular kinetic parameters (Cmax and AUC).
- The geometric means of AUC0-28d and Cmax of subjects in the below median weight group (≤75.8 kg) were 179% and 183% higher, respectively, than those of subjects in the above median weight group (>75.8 kg). Considering the higher inter-individual variability in cellular kinetics and the clinical response in the current study this may not trigger dosing adjustment, but future follow-up evaluation may be warranted to reaffirm bodyweight impact on PK parameters.
- Extrinsic factors such as prior hematogenic stem cell transplantation (HSCT) and lymphodepleting chemotherapy (fludarabine +cyclophosphamide) have no significant impact on PK parameters.
- The Cmax was higher by 312% and AUC0-28d was higher by 245% in subjects who received tocilizumab for CRS management as compared to subjects who did not receive tocilizumab. The median Tmax for tisagenlecleucel transgene was approximately 10 days, irrespective of use of tocilizumab.
- Overall, tisagenlecleucel exhibited a higher inter-subject PK variability and the cellular PK parameters in subjects with r/r FL are consistent with previous observation in patients with DLBCL.

Pharmacodynamics (PD):

- The median peak levels of cytokines such as interferon gamma, and IL-6 were higher in subjects who experienced CRS.
- The mean inflammatory markers and cytokines levels were comparable in responder versus non-responding subjects, except for mean ferritin levels, which were slightly higher in CR/PR subjects.
- B-cell aplasia is an on target off tumor pharmacodynamic effect of tisagenlecleucel, and there are potential PD interactions that may occur between

tisagenlecleucel, and agents administered as part of bridging and/or lymphodepletion conditioning regimens prior to tisagenlecleucel treatment. Rituximab is an anti-CD20 monoclonal antibody with a half-life of ~22 days and known to cause long term B-cell aplasia.

- In this study, all subjects received rituximab as a prior antineoplastic therapy, and the majority of subjects with measurable rituximab levels (at baseline) had non-detectable B cells.
- The geometric mean concentrations of rituximab (geometric-CV%) (ng/mL) at pre-dose, for responders (n=36) and non-responders (n=6) were 3360 (787.0%) ng/mL and 9810 (165.9%) ng/mL, respectively.
- At Day 28 post-infusion of tisagenlecleucel, the geometric mean concentration for responders (n=29) was 2230 (679.4%) ng/mL and for non-responders (n=6) it was 5230 (224.4%) ng/mL.
- At the time of study entry, 25 subjects (25.8%) had hypogammaglobulinemia. Sixteen subjects (16.5%) had prolonged depletion of normal B-cells/agammaglobulinemia post-tisagenlecleucel infusion.
- Thirty-three infused subjects received at least one dose of prophylactic immunoglobulin therapy post-infusion of tisagenlecleucel, and 11 of these subjects also receiving prophylactic administration prior to infusion.

Dose-Exposure and Dose-Response Analysis:

- The recommended tisagenlecleucel dose range in this study was 0.6 to 6.0×10^8 CAR-positive viable T-cells.
- The median dose administered was 2.06×10^8 CAR-positive viable T-cells (range: 0.1 to 6.0×10^8 cells) and 96% of the subjects received dose within the recommended range. Four subjects received tisagenlecleucel dose that were lower than recommended dose (range: 0.1 to 0.46×10^8 CAR-positive viable T-cells).
- The analysis of the relationship between total tisagenlecleucel cell dose and log-transformed cellular kinetic parameters (Cmax, and AUC0-28d) did not show strong relationship (R^2 <0.1).
- The logistic regression analysis of dose versus best overall response (BOR) relationship showed no statistically significant effect of dose on the BOR (OR: 1.67, 95% CI: 0.95 to 2.95).
- The dose-safety analysis showed a flat relationship indicating no impact of dose on any of the evaluated safety outcomes such as CRS, neurological events and cytopenia.
- Considering that there is no strong dose-exposure and dose-response relationship, the proposed dose of 0.6 to 6.0×10^8 CAR-positive viable T-cells is acceptable from clinical pharmacology perspective.

Exposure-Response Analysis:

- **Exposure-efficacy relationship:** Logistic regressions analysis was performed to evaluate the relationship between BOR and exposure parameters of tisagenlecleucel (Cmax and AUC0-28d). The probability of response appears to

be lower for lower exposure levels; however, no strong conclusion can be made due to limited number of non-responder subjects and higher variability of the cellular kinetic parameters.

- **Exposure-safety relationship:** No grade 3 or higher CRS was observed in adult r/r FL subjects within 8 weeks of infusion. Higher exposure metrics (AUC0-28d and Cmax) were associated with higher incidence of CRS (grade 1 or 2). The model estimated odds ratios for CRS events as a result of two-fold increase in the Cmax and AUC0-28d was 1.40 (95% CI: 1.13, 1.74) and1.37 (95% CI: 1.08, 1.72), respectively. These results indicate that statistically significant impact of exposure on CRS.

Immunogenicity Risk Assessments:

- Humoral immunogenicity was measured by determination of anti-murine CAR19 (antimCAR19) antibodies in serum samples pre- and post- tisagenlecleucel infusion. Cellular immunogenicity was evaluated based on assay that characterize the activation of T-cells in peripheral blood mononuclear cells collected from subjects in response to mCAR19-derived peptide pools.
- At baseline 66 % of the subjects (64/97) tested positive and 22.7% of the subjects (22/97) tested negative for anti-mCAR19 antibody. Treatment with tisagenlecleucel induced or boosted anti-mCAR19 antibodies in 27% of the subjects (27/94).
- The geometric mean AUC0-28d was similar in subjects with treatment induced or boosted anti-mCAR19 antibodies and antibody negative subjets post-tisagenlecleucel infusion.
- Cellular immunogenicity responses remained low (<1%) for most subjects at all time points evaluated, and it has no impact on PK or efficacy/safety related endpoints.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

All clinical trials pertinent to the evaluation of efficacy and safety are summarized in Table 9.

Table 9: Applicant – Listing of clinical trials relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen /schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Study to Support Efficacy and Safety								
CCTL019E2202 (ELARA)	NCT03568461	Phase II, single arm, multicenter, open label trial	Single infusion; 0.6 to 6.0 × 10^8 CAR-positive viable T cells	**Primary**: CRR per IRC **Secondary**: ORR, DOR, and PFS per IRC, OS, safety, cellular kinetics, immunogenicity, HRQoL	Enrolled set: median 16.59 months FU from infusion EAS: median 16.85 months mEAS: median 17.08 months	Total: 98 Infused: 97 EAS: 94 mEAS: 90	Adult patients with r/r FL with their disease meeting at least one of the following criteria: • Refractory to a second- or later-line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second- or later-line of systemic therapy • Relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion • Relapsed after autologous HSCT	30 sites across 12 countries: Australia (3), Austria (1), Belgium (1), France (2), Germany (3), Italy (2), Japan (3), Netherlands (1), Norway (1), Spain (2), UK (2), USA (9)

Supportive Study								
CCTL019A2101J	NCT02030834	Phase IIa, case study, open label trial	Single infusion; 1.0 to 5.0 × 10^8 CAR-positive viable T cells	**Primary**: ORR at 3 months **Secondary**: ORR, DOR, PFS, OS, safety, cellular kinetics, B cell depletion, recovery of humoral immunity	Median FU: 60.7 months	Total: 49 Treated and analyzed: 38 (FL: 14, DLBCL: 24)	Adult patients with refractory B-cell lymphomas (CD19+ DLBCL or FL) with no curative treatment options; a partial response to, or stable disease after, their most recent therapy; and limited prognosis (< 2 years of anticipated survival). Patients with FL who relapsed or were refractory to previous treatments were eligible if they had measurable progression of disease less than 2 years after second-line immunochemotherapy (excluding single-agent monoclonal antibody)	Single-center trial; USA
CRR: complete response rate; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; EAS: Efficacy Analysis Set; FL: follicular lymphoma; FU: follow-up; HRQoL: health-related quality of life; IRC: Independent Review Committee; mEAS: modified Efficacy Analysis Set; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; UK: United Kingdom; USA: United States of America								

The FDA's Assessment:

As noted in previous sections, only the study E2202 (ELARA) data were reviewed in benefit risk assessment for the treatment of proposed indication. The primary data from the study A2101J was not submitted. Hence, it was not taken into consideration for the regulatory decision making.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy of tisagenlecleucel in patients with r/r FL is supported by data from two clinical trials: a pilot Phase IIa trial, Study CCTL019A2101J (hereafter referred to as "Study A2101J") conducted by the University of Pennsylvania (Penn trial code: UPCC 13413), that was conducted first and provides supportive data and the Novartis-sponsored pivotal Phase II trial, Study CCTL019E2202 (hereafter referred to as "Study E2202").

8.1.1. Study E2202

Trial Design

The Applicant's Description:

Basic study design

Study E2202 is an ongoing, single-arm, global, multicenter trial that has enrolled adult patients ≥18 years of age with r/r FL (Grades 1, 2, 3A) meeting one of the following criteria:

- Refractory to a second or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second or later line of systemic therapy
- Relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion
- Relapsed after autologous HSCT

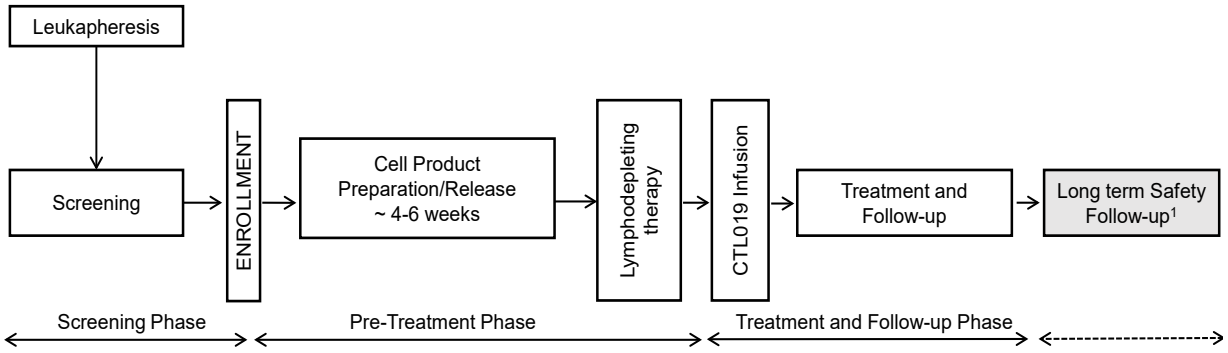
The study design as illustrated in Figure 1 includes the following major steps: screening, enrollment (with optional bridging therapy during manufacturing), infusion and follow-up phases. Prior to lymphodepletion and tisagenlecleucel infusion, the patient's disease is restaged to confirm baseline disease. The first efficacy assessment is measured at Month 3 and as per protocol, disease status is scheduled to be assessed every 3 months (±14 days) post-infusion until Month 12, then every 6 months (±14 days) thereafter, i.e., Months 3, 6, 9, 12, 18, 24, etc., (and at any time disease progression or relapse is suspected) until disease progression or relapse, start of new anticancer

therapies, death, lost to follow-up or withdrawal of consent.

The FDA's Assessment:

Although the study protocol outlines first disease assessment to be performed at 3 month (+/- 14 days), such assessments were performed at earlier time points in multiple subjects as deemed necessary by the investigators based on clinical circumstances. Therefore, these assessments were called Eval 1, 2, 3 etc. based on chronology, and not necessarily based on specific time points.

Figure 1: Applicant – Study E2202 design



1. Long term safety follow-up as per health authority guidance conducted under a separate LTFU protocol (CTL019A2205B).

Source: Study E2202 CSR-Table 9-1

Trial location

98 patients were enrolled in 30 sites across 12 countries - Australia (3), Austria (1), Belgium (1), France (2), Germany (3), Italy (2), Japan (3), Netherlands (1), Norway (1), Spain (2), United Kingdom (2), and United States of America (9).

Key inclusion/exclusion

Key inclusion criteria were:

- FL (grade 1, 2, 3A) confirmed histologically by central pathology review before tisagenlecleucel infusion
- FL meeting one of the following criteria:
  - Refractory to a second or later line of systemic therapy (including anti-CD20 antibodies and alkylating agents) or relapsed within 6 months after completion of a second or later line of systemic therapy
  - Relapsed during anti-CD20 antibody maintenance (following at least 2 lines of therapy as above) or within 6 months after maintenance completion
  - Relapsed after autologous HSCT
- Radiographically measurable disease at screening
- ECOG performance score of 0 or 1 at screening

- Must have a leukapheresis product of non-mobilized cells accepted for manufacturing

Key exclusion criteria were:

- Evidence of histologic transformation
- FL grade 3B
- Prior anti-CD19 therapy
- Prior gene therapy
- Prior adoptive T-cell therapy
- Prior allogeneic hematopoietic stem cell transplant
- Active CNS involvement by malignancy
- Investigational medicinal product within the last 30 days or five half-lives (whichever is longer) prior to screening

For the full list of criteria, please see Study E2202 CSR-Appendix 16.1.1-Protocol-Section 5.2.

The FDA's Assessment:

Out of all 98 enrolled subjects, there were 11 subjects who had inclusion criteria deviation. Three subjects were not r/r after two or more lines of systemic therapy (they had relapsed >6 months after the completion of their second line of therapy). One subject did not have histologically confirmed FL (grade 1, 2, 3a) by central pathology before tisagenlecleucel infusion. There were five subjects in whom documentation of disease at baseline was incomplete or missing. Detailed information about these subjects, including implication on risk benefit evaluation, are provided in the section of efficacy results.

Dose selection

Formal dose-escalation studies were not conducted. The recommended tisagenlecleucel dose of a single infusion of 0.6 to 6.0 × 10^8 CAR-positive viable T cells (non-weight based) is in accordance with the product labelling for the r/r DLBCL indication in adult patients. This same dose range was used in the pivotal Study E2202 for r/r FL, and the dose administered in Study A2101J was within the dose range in Study E2202.

The FDA's Assessment:

Of the 90 subjects included in FDA's primary efficacy analysis, 82 subjects were included in the per protocol set. Four subjects received dose below the recommended dose range (0.6 to 6.0 x 10^8 CAR-positive viable T cells). One of these subjects had a BOR of CR, one a BOR of PR, one had PD and the one had unknown BOR. Majority of the subjects, (96%, 86/90) included in the primary efficacy population received the proposed recommended dose. The other four subjects were excluded from the per protocol set since they had protocol

deviation either due to missing or incomplete documentation of disease at baseline. Please see the table below for details.

Table 10: FDA Reviewer – Subjects who received out of specification dose and their best objective response (BOR)

Subject ID	BOR	CTL019 dose infused ($X10^8$ cells)	Reason for exclusion from PPS
(b) (6)	CR	0.8 (Within range)	Missing or incomplete documentation of disease at baseline (Baseline PET was not performed; but the measurable disease was confirmed at baseline by CT scan.
	CR	2.8 (Within range)	Missing or incomplete documentation of disease at baseline (No BM aspirate/biopsy was performed at baseline, see response adjudication for further detail about BOR of CR)
	PD	0.4 (Below range)	1st attempt terminated; 2nd attempt low dose
	Unknown	0.36 (Below range)	Low dose
	PR	1.8 (Within range)	Missing or incomplete documentation of disease at baseline (No BM aspirate/biopsy was performed at baseline)
	PR	2.6 (Within range)	Missing or incomplete documentation of disease at baseline (No BM aspirate/biopsy was performed at baseline)
	CR	0.46 (Below range)	Low dose
	PR	0.2 (Below range)	Low dose
Source: FDA review of ADSL, ADEX, ADEFIRC dataset, and Case Study Report			

As noted above, four subjects who were treated with lower than recommended dosage of tisagenlecleucel (range 0.2 to 0.46 x 108 viable CAR T cells) had variable BOR (one

CR, one PR, one PD and one unknown BOR). No clear relationship with these variation in dosing with the BOR was observed. The inclusion of these subjects in primary efficacy population did not affect the overall conclusion of the recommended dose and the efficacy results, since over 95% subjects received tisagenlecleucel in the recommended dose range.

Study treatments

Bridging therapy

When administering a bridging therapy during the Pre-treatment phase, the Investigator followed the recommendations described under 'Prohibited concomitant therapy' in Study E2202 CSR-Appendix 16.1.1-Protocol-Section 6.4.1.

A PET-CT scan was performed after bridging therapy and prior to tisagenlecleucel infusion, except when the bridging therapy consisted of steroids only. Patients with no measurable disease at baseline after bridging therapy still received tisagenlecleucel infusion.

The FDA's Assessment:

Of the 90 subjects included in FDA's primary efficacy analysis, 40 subjects (45%) were treated with bridging therapies. The most commonly used agents (in ≥ 5% of subjects) were rituximab (21.6%), dexamethasone (11.3%), gemcitabine (10.3%), oxaliplatin (7.2%), prednisolone (7.2%), etoposide (6.2%), cyclophosphamide (5.2%), and vincristine (5.2%).

Lymphodepleting chemotherapy

Prior to tisagenlecleucel infusion, all patients were required to receive lymphodepleting (LD) chemotherapy. This step was to be omitted in case of significant cytopenia (e.g., WBC <1000 cells/μL, absolute lymphocyte count <200 cells/μL) or any condition that, in the Investigator's opinion, precluded LD chemotherapy. The purpose of this chemotherapy was to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of the administered CAR-positive viable T cells.

LD chemotherapy started 1 week before tisagenlecleucel infusion so that the CAR-positive viable T cells were given 2 to 6 days after completion of the LD chemotherapy. The chemotherapy start date varied based on the selected chemotherapy. For LD chemotherapy, cyclophosphamide-based regimens were preferred agents due to the vast experience with the use of these agents in facilitating adoptive immunotherapy. The first option as LD regimen was:

- Fludarabine (25 mg/m^2 IV daily for 3 doses) and cyclophosphamide (250 mg/m^2 IV daily for 3 doses starting with the first dose of fludarabine)

If there was previous grade 4 hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen,

then the following regimen was allowed:

- Bendamustine 90 mg/m^2 IV daily for 2 days

No other regimen was allowed for LD chemotherapy.

The FDA's Assessment:

All infused subjects as well as all subjects included in the primary efficacy analysis, received LD chemotherapy prior to tisagenlecleucel infusion. Most subjects received fludarabine + cyclophosphamide.

Table 11: FDA Reviewer – Lymphodepleting regimens used in study E2202

Lymphodepleting chemotherapy	All infused subjects (n=97)	Primary efficacy set (n=90)
Fludarabine+cyclophosphamide	92 (95%)	85 (95%)
Bendamustine	5 (5%)	5(5%)
Source: Review of ADCM dataset and Case Study Report, Table 14.3-2.1		

Tisagenlecleucel infusion

The recommended dose is 0.6 to 6.0 × 10^8 CAR-positive viable T-cells administered via a single infusion. Before tisagenlecleucel was administered, a preinfusion evaluation and some additional safety procedures were performed.

The FDA's Assessment:

Tisagenlecleucel was administered at the dose of 0.6 to 6.0 x 10^8 CAR positive viable T cells. The dose utilized was based on the dose used in subjects with r/r DLBCL in the phase II Study C2201. All treated subjects (n=97), except for 4, received tisagenlecleucel within the targeted dose range. Those four subjects received tisagenlecleucel products that were OOS due to a lower dose than specified as per protocol (OOS range: 0.2 to 0.46×108 CAR-positive viable T-cells). The median dose administered was 2.06×10^8 CAR-positive viable T-cells (range: 0.2 to 6.0×10^8 cells). The median total viable cell count was 12×10^8 cells (range: 0.4 to 34.0 ×10^8 cells).

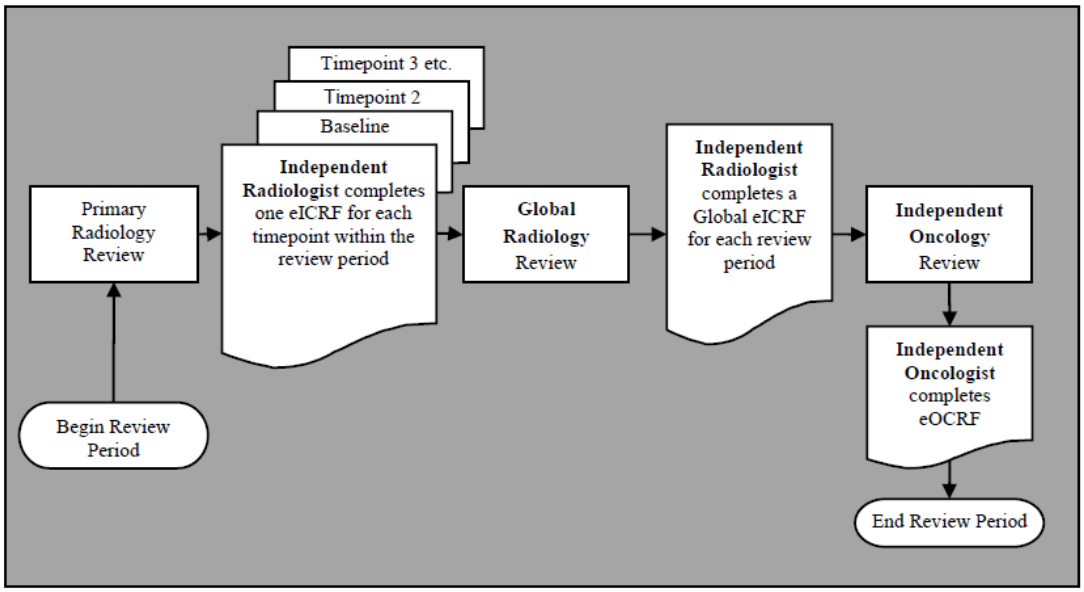
Assessment of efficacy

Efficacy was evaluated by an Independent Review Committee using the Lugano classification 2014 (Barrington et al 2014, Cheson et al 2014). A steering committee was established comprising of investigators participating in the trial and Novartis representatives from the clinical trial team. Baseline disease and the disease response

were assessed at prespecified timepoints by the local investigators as well as by the IRC.

(b) (4), a third-party company, was contracted to provide independent assessment of imaging studies and relevant clinical data for the E2202 study. The independent review process included multi-phase review including timepoint by timepoint blinded radiology review by independent radiologists, followed by a global radiology review and then oncology review by independent oncologists. The independent oncologists were provided with a clinical dossier for each patient at each timepoint extracted from the eCRF containing information on any clinical findings (examination), BM aspirate and/or biopsy, tumor biopsies, fluid collections, CSF samples, prior/concomitant surgery/procedures, or any other clinically relevant information. The oncologists reviewed the final radiology assessment and available clinical data for a subject and provided the final tumor assessment for each visit. To ensure the quality and integrity of the process, secondary radiology variability review was repeated for a subset of subjects to determine intra-reader and/or inter-reader agreement. Furthermore, secondary review of the original reads by both independent radiologists as well as independent oncologists were performed.

Figure 2: Efficacy Assessment by Independent Review Committee



Source: Study E2202 Independent Review Charter

Subject completion, discontinuation, or withdrawal

Discontinuation of study treatment

Tisagenlecleucel infusion could be discontinued while administering if, in the Investigator's opinion, its continuation was detrimental to the patient's safety. Patients

who discontinued from tisagenlecleucel treatment were not considered withdrawn from the study and were continued to be followed as per assessment schedule.

If a patient developed a condition that precluded tisagenlecleucel infusion while or after receiving LD chemotherapy but before the tisagenlecleucel infusion, the patient was to be prematurely discontinued. This was done at the judgment of the Principal Investigator, and could include for example, the occurrence of an intercurrent illness requiring the institution of systemic immunosuppression. In such a case, all the assessments listed for the end of study (EOS) visit were to be performed.

Discontinuation from study

Patients could voluntarily withdraw/discontinue from the study for any reason at any time, but the EOS assessments were to be performed as soon as possible. Patients may be withdrawn from the study due to non-compliance, voluntary withdrawal, or if they were lost to follow up.

Withdrawal of consent

Withdrawal of consent could occur at any time when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the Investigator was supposed to make an effort to understand the primary reason for the patient's decision to withdraw the consent and record this information.

Study completion and long-term follow up

The EOS will occur when all patients have completed Month 24 evaluation or discontinued prematurely. Patients who have completed their Month 24 visit before the EOS will be followed for assessments at onsite visits every 6 months until the EOS. Study completion is defined as last patient last visit.

For all patients who received a tisagenlecleucel infusion, follow-up for survival every 3 months until EOS was required. After the end of this study, patients will continue to be followed for long term safety, efficacy and survival under the long-term follow-up protocol CCTL019A2205B (a separate informed consent form will be provided for this protocol).

Study Endpoints

The Applicant's Description:

Primary endpoint

The primary endpoint is CRR per IRC. The CRR was defined as the proportion of

patients with a BOR of CR recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever came first.

CRR was chosen as the primary endpoint as there is a demonstrated robustness of this endpoint as a surrogate for PFS and OS. Available data indicates that CR is associated with longer PFS and OS compared with PR or non-responders (Jiménez-Ubieto et al 2017, Salles et al 2017).

In patients with previously untreated FL, a large meta-analysis of 13 randomized trials with data from 3837 patients demonstrated that CR30 (CR at 30 months) strongly correlated with PFS (Shi et al 2017). A minimum 11% absolute improvement in CR30 from a 50% control rate predicted a significant treatment effect on PFS (hazard ratio: 0.69).

Currently approved non-CAR-T treatments in r/r FL were associated with low CRR (<39% with anti-CD20 therapies and <20% with PI3K-inhibitor therapies).

CAR-T therapies previously demonstrated high and durable CRR in B-cell lymphomas (e.g., large B-cell lymphoma indications for tisagenlecleucel, axicabtagene ciloleucel, and lisocabtagene maraleucel including FL). In the Phase IIa pilot Study A2101J (Schuster et al 2017), the median PFS was 26.2 months and the estimated PFS rate at 5 years after infusion was 43% (95% CI: 18, 66), after 60.7 months of follow-up. Furthermore, the Kaplan Meier plot for PFS demonstrates a plateau from 36 months.

These data demonstrate that the achievement of CR translates into durability of responses and therefore favorably impacts the PFS in this patient population.

Secondary efficacy endpoints

The secondary efficacy endpoint are defined in Table 12 below.

Table 12: Applicant – Secondary efficacy endpoints

Endpoint	Definition
Overall response rate	The proportion of patients with a best overall disease response of CR or PR recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever came first
Duration of response	Applies only to patients whose best overall disease response was CR or PR. It is the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to FL.
Progression-free survival	The time from the date of first tisagenlecleucel infusion to the date of event defined as the first documented progression or death, due to any cause
Overall survival	Time from date of first tisagenlecleucel infusion to date of death due to any reason
Health-related QoL	Summary scores of patient reported outcomes measured by SF-36 version 2, EQ-5D-3L and FACT-Lym quality of life questionnaires

The FDA's Assessment:

The primary end point of the E2202 study was complete response rate (CRR). The FDA's primary determination of efficacy is based on overall response rate, further supported by durability of response. Overall response rate (ORR) is an intermediate endpoint reasonably likely to predict the clinical benefit. Therefore, using ORR, supported by CR rate, along with DOR in indolent and serious diseases like FL, is acceptable to support a determination of efficacy. As communicated during pre-BLA meeting, efficacy will be based on first 90 consecutively treated subjects who have baseline disease as confirmed by IRC, received treatment with tisagenlecleucel and have a minimum of 9 months follow up from first objective response or have otherwise discontinued earlier. Accelerated approval of tisagenlecleucel can be considered based on robust and durable ORR in adult patients with relapsed or refractory FL after two or more prior lines of systemic therapies. Continued approval will be contingent upon demonstration of meaningful clinical improvement through a randomized clinical trial or trials.

Statistical Analysis Plan and Amendments

The Applicant's Position:

Data included in the analysis

The extended follow-up analysis included in the sBLA was performed after 90 patients received tisagenlecleucel infusion and were followed for at least 12 months from infusion (Day 1) or discontinued earlier.

All statistical analyses were performed using data collected in the database up to the cutoff date of 29-Mar-2021. All data with an assessment date or event start date (e.g., vital sign assessment date or start date of an AE) prior to or on the cut-off date were included in the analysis. Any data collected beyond the cut-off date was not included in the analysis and not used for any derivations.

Data sets

The following data or analysis sets were defined:

Screened set

The Screened set comprised all the patients who signed informed consent and were screened for the study.

Enrolled set

The Enrolled set comprised of all patients who were enrolled in this study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' leukapheresis product was received and accepted by the manufacturing facility.

Tisagenlecleucel infused set

The Tisagenlecleuce infused set comprised of all the patients who received tisagenlecleucel.

Efficacy analysis set (EAS)

The EAS comprised of all patients who received tisagenlecleucel and had measurable disease at baseline per IRC. Non-measurable disease at baseline is defined as absence of index lesion at baseline disease evaluation (i.e., no disease at baseline). The EAS was used for all efficacy analyses as per protocol.

Modified efficacy analysis set (mEAS)

The mEAS included the first 90 patients who received tisagenlecleucel and had measurable disease at baseline per IRC. The first 90 patients were followed for 12 months after infusion or have discontinued earlier.

Safety set

The Safety set comprised of all patients who received tisagenlecleucel. The Safety set was used for all safety analyses. The Safety set contains the same patients as the Tisagenlecleucel infused set.

Per-protocol set (PPS)

The PPS consisted of a subset of patients in the EAS who had diagnosis of FL at baseline and received the recommended dose.

Protocol deviations leading to exclusion from the PPS included:

- No diagnosis of FL at baseline
- Missing or incomplete documentation of disease at baseline
- Receiving a dose less than the recommended minimum dose of 0.6×10^8 CAR-positive viable T cells.

Cellular kinetic analysis set (CKAS)

The CKAS consisted of patients in the EAS who provided an evaluable cellular kinetic profile (at least 1 cellular kinetic parameter). The CKAS was used for summaries (tables and figures) of cellular kinetic data. The Tisagenlecleucel infused set was used for listings of cellular kinetic data.

Tocilizumab pharmacokinetic analyses set (TPAS)

The TPAS consisted of patients in the Tisagenlecleucel infused set who took at least one dose of tocilizumab and provided at least one tocilizumab PK concentration.

Previous analyses

Interim analysis

An interim analysis for overwhelming efficacy was pre-planned per the protocol when approximately 50 patients (55.6%) of the planned 90 patients received tisagenlecleucel infusion and have either completed 6 months from study Day 1 infusion or discontinued earlier. As 97 patients (and not the planned 90 patients) were infused and 52 patients (and not the planned 50 patients) were included in the interim analysis, the efficacy boundaries were re-calculated based on the actual number of patients using the pre-specified alpha-spending. The primary endpoint was met in this analysis. By the time of the interim analysis (data cutoff date of 26-May-2020), enrollment into the study was completed and all enrolled patients were treated or discontinued prior to infusion. Therefore, the study was not stopped for outstanding efficacy.

Primary analysis

The primary analysis was planned and performed when first 90 consecutively treated patients were followed for at least 6 months or discontinued earlier (data cutoff date of

28-Sep-2020).

Changes in planned analysis

No major changes in analysis occurred. There were two minor changes to the planned analysis before the database lock:

- The “Full analysis set” was renamed as “Tisagenlecleucel infused set” for clarity, since this is a single-arm, open-label study, “Infused set” is a more precise term.
- The censoring reason "Event documented after at least 2 missing tumor assessments" for the analysis of the secondary endpoints DOR and PFS was removed. Disease progression or death after 2 or more tumor missing assessments was counted as event following standard project rule and assuming that missing assessments were unlikely to correspond to disease progression in FL.

Additional analyses to assess the impact of COVID-19 pandemic

The number and percentage of patients enrolled, infused with tisagenlecleucel, and discontinued in the pre-COVID-19 pandemic period, during the COVID-19 pandemic period, and the post-COVID 19 pandemic period (if applicable) were summarized by region and country on the Enrolled set. The corresponding pandemic periods were defined based on the start and end date of the pandemic in the respective region/country.

Demographics, baseline characteristics and primary disease history were summarized by pandemic set on the tisagenlecleucel infused set to assess the impact of the COVID 19 pandemic on the study population considering 01-Mar-2020 as the start of the pandemic in rest of the world countries:

- Pre-pandemic set: Patients who completed the end of treatment and follow-up period or discontinued the trial before the pandemic start date in their region/country.
- During pandemic set: Patients with at least one on-treatment assessment or treatment-emergent event during the pandemic dates as defined for their region/country.
- After-pandemic set: Patients who were enrolled (based on the screening completion date) in the study after the pandemic end date in their region/country.

Number and percentage of patients with COVID-19 related protocol deviations were summarized on the tisagenlecleucel infused set and were listed for the Enrolled Set.

Listing of suspected or confirmed SARS-CoV-2 infections was produced. Additionally, concomitant medications were listed separately for patients infected with COVID-19.

The FDA’s Assessment:

Of the 98 enrolled subjects, FDA's primary efficacy analysis was performed in first 90 subjects who received tisagenlecleucel, had measurable disease at baseline per IRC, and had a minimum of 9 months follow up from first objective response or would have discontinued earlier. Of note, as agreed upon during the preBLA meeting, one of these 90 subjects had less than 9 month follow up, since the subject missed Month 3 assessment due to COVID-19 pandemic. Furthermore, the response rates in the primary efficacy population were also compared with that in intention to treat population (i.e., all leukapheresed population, n=98). The safety analysis population included all 97 subjects who were treated with tisagenlecleucel.

Protocol Amendments

The Applicant's Position:

There were no amendments to the protocol.

Changes in the conduct of the study due to COVID-19

To minimize the impact of COVID-19 on patients' safety and to maintain trial research integrity the Novartis study team released recommendation to help sites with the conduct of the study, including remote safety visits (i.e., by phone, or by an alternative health care professional), safety labs and efficacy assessments done by local laboratory and local facilities.

For PRO data collection, the use of paper back-up questionnaires in interview mode was also authorized, both at site, and also when patients were unable to visit the site in person and complete the questionnaires using a tablet due to COVID-19 disruption. For patients who were unable to visit the site, the designated site personnel had administered the questionnaires over the phone to the patient and the patient's responses were recorded. The completed paper questionnaires were sent to the ePRO vendor for data entry and subsequently flagged in the database for tracking purposes.

Additionally, sites were asked to follow the most recent version of European Society for Blood and Marrow Transplantation (EBMT), Society for Immunotherapy of Cancer (SITC) and American Society for Transplantation and Cellular Therapy (ASTCT) guidelines for COVID-19 to handle patients treated with cellular and CAR therapy. Whenever possible, testing for the presence of COVID 19 virus was highly recommended in patients prior to start of LD chemotherapy.

Changes in the study conduct compared to the protocol due to COVID-19 were reported as protocol deviations. This included not only those protocol deviations defined already at study start but also additional new COVID-19 protocol deviations such as:

missing visits
changes in procedures and discontinuations
obtaining the PRO assessment data
planned visits not done at sites

treatment delayed
patient discontinuation due to COVID-19 situation

All COVID-19 related protocol deviations were flagged as related to COVID-19 and were classified as follows:

- COVID-19 health status related (i.e., patient's infection led to this protocol deviation)
- COVID-19 situation: Site issue (e.g., site closed, personnel not available)
- COVID-19 situation: Lockdown/quarantine of patient (e.g., site was active, but patient was not allowed to come)
- COVID-19 situation: Patient concern (e.g., site was active, and patient could visit but refused to visit/complete the assessment)
- COVID-19 situation: Other (e.g., situation not already covered by the information above)

The FDA's Assessment:

In view of the missing efficacy data, lack of flags essential to perform timely review, the applicant was requested to submit revised efficacy datasets. The substantial revision in the dataset prompted a major amendment to the supplement, resulting in extension of the review time by 3 months.

Compliance with Good Clinical Practices

The Applicant's Position:

The study was conducted according to ICH E6 Guideline for Good Clinical Practice that have their origin in the Declaration of Helsinki.

Reviewer's comments: The applicant has made explicit statement of Good Clinical Practice affirming that all studies were conducted under the supervision of an IRB and with adequate informed consent procedures.

Financial Disclosure

The Applicant's Position:

Details of financial disclosure are presented in Section 17.2.

The FDA's Assessment:

The applicant has submitted signed financial disclosure forms FDA 3454 and 3455 per 21 CFR 54.4 (a)(1) and (3) under module 1.3.4 of the application.

Patient Disposition

The Applicant's Position:

At the time of the data cut-off for this extended follow-up analysis (29-Mar-2021), 98 patients were enrolled in the study (Table 13).

All enrolled patients, except for one, received their tisagenlecleucel infusion. One patient who did not receive the tisagenlecleucel infusion discontinued from the study due to physician decision; this patient achieved a complete response prior to infusion which was likely attributed to their last line of therapy (copanlisib) administered before study entry (Study E2202 CSR-Listing 16.2.5-3.1).

Of the 97 patients who were infused, 80 patients were ongoing in the study at the time of the data cut-off and 17 patients had discontinued the study. The reasons for discontinuation from the study were (Study E2202 CSR-Listing 16.2.1-1.2):

- Death (n = 7) (Study E2202 CSR-Table 14.3.1-3.1):
  - 5 patients died due to the study indication
  - 1 patient died in ongoing complete response due to late onset of CRS (1-year post-infusion) by Investigator assessment (Study E2202 CSR-Section 14.3.3)
  - 1 patient died due to euthanasia chosen for progressive neurological symptoms due to PML. The patient was in ongoing complete response at time of death
- Physician decision (n = 4)
  - 1 patient (Patient (b) (6)) developed bilateral COVID-19 pneumonia post-infusion, hence the treating physician decided to enroll the patient onto a COVID-19 clinical trial
  - 3 patients were discontinued after PD, one of whom started a new investigational therapy in another clinical trial
- Patient decision (n = 5)
  - 4 patients discontinued after disease progression 2 patients discontinued due to disease progression
  - 1 patient opted to withdraw to move to a closer healthcare facility
- Lost to follow-up (n=1, almost one-year post-infusion)

Table 13: Applicant - Study disposition (Enrolled set)

	All patients N=98 n (%)
Patients enrolled	**98 (100.0)**
Patients treated	97 (99.0)
Discontinued prior to tisagenlecleucel infusion	1 (1.0)
Reason for discontinuation	
Physician decision	1 (1.0)
Study ongoing[1, 2]	80 (81.6)
Discontinued study	18 (18.4)
Reason for discontinuation	
Death	7 (7.1)
Physician decision[3]	5 (5.1)
Subject decision	5 (5.1)
Lost to follow-up	1 (1.0)

[1] Ongoing at the time of the data cut-off date 29-Mar-2021

[2] Study ongoing includes patients who completed or discontinued the treatment phase and are still being followed for survival under study protocol.

[3] One patient who did not receive the tisagenlecleucel infusion discontinued from the study due to physician decision

Source: Study E2202 CSR-Table 14.1-1.2, Table 14.1-1.3

The FDA's Assessment:

As depicted in the Table above, one subject underwent leukapheresis with the intention to treat with tisagenlecleucel. However, during the baseline disease evaluation, the subject was found to have complete response to previously administered antineoplastic therapy. Therefore, as per the investigator's decision, the subject did not receive the treatment, and discontinued from the study. There was no manufacturing failure in this study.

Protocol Violations/Deviations

The Applicant's Position:

In the Enrolled set (n=98), protocol deviations were reported in 58 patients (59.2%); however, these deviations were typically minor and were not considered to impact the overall conclusions of the study. The most common protocol deviations reported in ≥ 10 patients fell into the following categories (Study E2202 CSR-Table 14.1-3.1):

- 'Other deviations', were reported in 50 patients (51.0%). The most common subcategories reported in ≥ 10 patients were:
    - 18.4% of the patients missed ≥ 3 consecutive PK timepoints (qPCR and/or

flow cytometry)
    - In 17.3% of the patients, ≥ 3 consecutive PRO questionnaires were not collected as per protocol
    - In 14.3% of the patients, safety assessments were not performed as per protocol
    - In 13.3% of the patients, response assessments were not performed as per protocol
- Treatment deviations in 15 patients (15.3%) – the majority were due to 'influenza testing not performed within 10 days prior to planned tisagenlecleucel infusion'
- Any inclusion criteria deviation in 11 patients – of which, **3 patients were not r/r after ≥ 2 lines of therapy (the patients had relapsed >6 months after completion of their second-line of therapy)**, in 3 patients oxygen saturation by pulse oximetry was not done, and in 2 patients, study procedures were performed prior to obtaining signed ICF (ECG was performed in 1 patient and ECG and viral test were performed in the second patient) and the other deviations were reported by one patient each

The study enrollment was completed during the pre-pandemic phase and the majority of the patients (n=82) were infused during the pre-pandemic phase (Study E2202 CSR-Table 14.1-1.4).

Demographics and baseline characteristics are summarized by pandemic period in Study E2202 CSR-Table 14.1 4.1cvd and disease history and prior antineoplastic therapies by pandemic period is presented in Study E2202 CSR-Table 14.1-5.1cvd. The tables show that there was no impact of pandemic on patient enrolment and study population.

Protocol deviations during the COVID-19 pandemic occurred mainly due to patient concern (23.7%), lockdown (11.3%), site issue (11.3%), and patient health status (2.1%) (Study E2202 CSR-Table 14.1 3.4, Listing 16.2.2-2). These deviations included:

- In 46 patients, visits were not done at the study site due to patient concern (n=19), lockdown (n=10), other issues (n=10) and site issues (n=7).
- 11 patients missed visits due to patient concern (n=5), lockdown (n=2), other issues (n=2), health status (n=1) and site issues (n=1)
- In 9 patients assessment/procedure changed due to other reasons (n=5), site issues (n=3) and patient concern (n=1)
- 1 patient discontinued the study due to COVID-19 infection

Note: A patient could have multiple protocol deviations.

These deviations did not have an impact on the primary efficacy endpoint at the time of the current extended follow-up analysis.

<u>The FDA's Assessment:</u>

Most protocol deviations were minor and were very unlikely to substantially affect the

conclusion of the results. Three subjects were not r/r after two prior lines of systemic therapy (these subjects had relapsed more than 6 months after the completion of their second line of therapy). In 13% of the subjects, the response assessments were performed outside of the protocol allowed time windows. Similarly, out-of-window safety assessments were performed in 14% of enrolled subjects.

Table 14: FDA Reviewer – Important protocol deviations in study E2202

Subject ID	Deviation	Potential impact on efficacy assessment
(b) (6)	The subject relapsed 11 months after the last line of therapy. The subject was included in the primary efficacy analysis population. The subject had a BOR of CR.	Recommend including this info in the label (Applicant has agreed)
	The subject relapsed 12 months after the last line of therapy. The subject was included in the primary efficacy analysis population. The subject had a BOR of CR.	Recommend including this info in the label (Applicant has agreed)
	The subject relapsed 14 months after the last line of therapy. The subject was not included in the primary efficacy analysis population due to absence of measurable disease at baseline.	No
	A tumor sample was collected at diagnosis (Oct 2014) which showed follicular lymphoma grade 3a. At screening (Jan 2020), the tumor biopsy was not diagnostic (absence of tumor cells), and thus was not sent for central review. The marrow at screening ((b) (6)) showed marrow involvement with 25% follicular lymphoma grade 3a per local pathology review. By the time the applicant was informed, the product was already manufactured. Therefore, the subject was treated on the basis of diagnosis by bone marrow. The subject was included in the primary efficacy population, and had a BOR of CR.	No
	Baseline PET CT was not performed. The measurable disease at baseline was confirmed by CT with contrast. The subject was included in the primary efficacy population, and had BOR of	No

	CR.	
(b) (6)	No BM aspirate/biopsy was performed at screening.	Necessary response adjustment was performed based due to absence of BM at screening.

The Applicant's Position:

The demographic and baseline disease characteristics were representative of the r/r FL patient population as defined by the protocol criteria. The demographics of the population in the EAS and mEAS were consistent with the Enrolled set (Table 15).

Table 15: Applicant/FDA Reviewer: Demographics and baseline characteristics

Demographic variable	All Leukapheresed population N=98 n (%)	Primary efficacy population N=90 n (%)
Age at study entry (years)		
Mean (SD)	56.5 (10.34)	56.7 (10.64)
Median	57.5	58.0
Q1-Q3	49.0-64.0	49.0-65.0
Min-Max	29-73	29-73
Age category - n (%)		
18-<65 years	74 (75.5)	66 (73.3)
65-<85 years	24 (24.5)	24 (26.7)
Sex - n (%)		
Male	65 (66.3)	62 (68.9)
Female	33 (33.7)	28 (31.1)
Race - n (%)		
White	74 (75.5)	70 (77.8)
Asian	13 (13.3)	9 (10.0)
Japanese	9 (9.2)	7 (7.8)
Indian	2 (2.0)	2 (2.2)
Missing	2 (2.0)	0
Black or African American	1 (1.0)	1 (1.1)
Missing	10 (10.2)	10 (11.1)
Ethnicity - n (%)		
Not Hispanic or Latino	84 (85.7)	77 (85.6)
Hispanic or Latino	3 (3.1)	2 (2.2)
Not reported	11 (11.2)	11 (12.2)

Demographic variable	All Leukapheresed population N=98 n (%)	Primary efficacy population N=90 n (%)
ECOG performance status - n (%)		
0	56 (57.1)	51 (56.7)
1	39 (39.8)	37 (41.1)
2[1]	3 (3.1)	2 (2.2)

[1] These three patients had ECOG status of 2 recorded just before receiving tisagenlecleucel infusion, and not at the time of signing the ICF.
SD: standard deviation
Source: Study E2202 CSR-Table 14.1-4.1, Table 14.1-4.2, Table 14.1-4.3

The FDA's Assessment:

The demographic characteristics of the subjects included in the FDA's primary efficacy analysis were similar to all leukapheresed (i.e., intention to treat) population. Of note, there was limited representation of African American, Hispanic, and patients with other ethnic background.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics were consistent across the Enrolled set and mEAS/Primary efficacy population (Table 16). Most of the patients presented with advanced FL (Stage III or IV) at study entry. Patients were heavily pretreated with multiple prior lines of antineoplastic therapy (median of 4 prior lines [range: 2 to 13]).

Table 16: Applicant/FDA reviewer: Primary disease history and prior antineoplastic therapies

Disease history	All leukapheresed population N=98 n (%)	Primary Efficacy Population N=90 n (%)
Diagnosis of disease – n (%)		
Follicular lymphoma	98 (100)	90 (100)
Stage at initial diagnosis – n (%)		
Stage I	6 (6.1)	5 (5.6)
Stage II	13 (13.3)	13 (14.4)
Stage III	21 (21.4)	19 (21.1)
Stage IV	57 (58.2)	52 (57.8)
Missing	1 (1.0)	1 (1.1)
Stage at time of study entry – n (%)		
Stage I	3 (3.1)	2 (2.2)
Stage II	11 (11.2)	10 (11.1)

Disease history	All leukapheresed population N=98 n (%)	Primary Efficacy Population N=90 n (%)
Stage III	26 (26.5)	25 (27.8)
Stage IV	58 (59.2)	53 (58.9)
Bone marrow involved at study entry – n (%)		
Yes	37 (37.8)	35 (8.9)
No	60 (61.2)	54 (60.0)
Missing	1 (1.0)	1 (1.1)
Histological grade at study entry – n (%)		
Grade 1-2 (low grade)	88 (89.8)	81 (90.0)
Grade 3A	10 (10.2)	9 (10.0)
Were any extralymphatic sites involved by lymphoma at study entry – n (%)		
Yes	30 (30.6)	27 (30.0)
No	68 (69.4)	63 (70.0)
FLIPI at study entry[1] – n (%)		
Low	18 (18.4)	16 (17.8)
Intermediate	21 (21.4)	18 (20.0)
High	59 (60.2)	56 (62.2)
Absolute lymphocyte count (ALC) at study entry (10^9/L)		
n	97	90
Mean (SD)	2.4 (1.51)	2.4
Median (min – max)	1.9 (0.2 - 7.0)	2.0 (0.2 - 7.0)
Number of prior lines of antineoplastic therapy		
Median (min – max)	4.0 (2.0 – 13.0)	4.0 (2.0 – 13.0)
Number of prior lines of antineoplastic therapy – n (%)		
2	24 (24.5)	22 (24.4)
3	21 (21.4)	19 (21.1)
4	25 (25.5)	22 (24.4)
≥5	28 (28.6)	27 (30.0)
6	7 (7.1)	7 (7.8)
7	5 (5.1)	5 (5.6)
9	1 (1.0)	1 (1.1)
13	1 (1.0)	1 (1.1)
Progression of disease within 24 months (POD24)[2] from first-line anti-CD20 mAb containing therapy - n (%)		
POD24 group	61 (62.2)	59 (65.6)

Disease history	All leukapheresed population N=98 n (%)	Primary Efficacy Population N=90 n (%)
Non-POD24 group	36 (36.7)	31 (34.4)
Missing	1 (1.0)	0
Bulky disease at baseline [3] - n (%)		
Yes	62 (63.3)	58 (64.4)
No	36 (36.7)	32 (35.6)
Treatment density[4]		
Mean (SD)	1.73 (1.165)	1.65 (1.159)
Median (min – max)	1.40 (0.14 – 5.65)	1.31 (0.14 – 5.65)

[1] FLIPI includes 5 labelled prognostic factors; FLIPI = sum (where prognostic factor = 'Yes'); Low: 0-1 criteria met; intermediate: 2 criteria met; high: 3 or more met.
[2] POD24: subjects with primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb containing treatment.
[3] Bulky disease defined per IRC as imaging showing any nodal or extra nodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.
[4] Treatment density: derived as time from initial diagnosis to study entry (year)/number of lines of prior therapy
SD: standard deviation
Source: FDA reviewer's review of ADSL dataset and CSR-Table 14.1-5.1, Table 14.1-5.2, Table 14.1-5.3

The FDA's Assessment:

The disease characteristics in the primary efficacy population were similar to those in all leukapheresed population. Majority of the subjects had advanced disease (Stage III and IV) at study entry, and were heavily pretreated. The subjects had received various prior lines of therapies as listed in Table 17.

Table 17: FDA Reviewer - Prior antineoplastic therapies received by subjects enrolled and included in primary efficacy evaluation

Prior Therapies	All leukapheresed population, N=98 (%)	Primary efficacy population, N=90 (%)
Anti-CD20 mAb	98 (100)	90 (100)
Alkylating agents	98 (100)	90 (100)
Bendamustine	66 (67.3)	61 (67.8)
Other	96 (98.0)	88 (97.8)
Anthracyclines	89 (90.8)	81 (90.0)

Purine analogues	2 (2.0)	2 (2.2)
PI3K inhibitor	21 (21.4)	18 (20.0)
Lenalidomide	22 (22.4)	21 (23.3)
Investigational drugs	17 (17.3)	17 (18.9)
BTK inhibitors	4 (4.1)	4 (4.4)
Combination of anti-CD20 mAb (any regimen) + alkylating agent (any regimen)	98 (100)	90 (100)
Combination of anti-CD20 mAb + alkylating agent (within same regimen)	97 (99.0)	89 (98.9)
RCHOP (within same regimen)	42 (42.9)	41 (45.6)
RCVP (within same regimen)	47 (48.0)	46 (51.1)
Bendamustine + anti-CD20 mAb (within same regimen)	61 (62.2)	56 (62.2)
Lenalidomide + Rituximab (within same regimen)	17 (17.3)	16 (17.8)
Prior autologous HSCT	36 (36.7)	32 (35.6)
Source: FDA Reviewer's review of ADCM dataset, and CSR Table 10.4.3 and 14.1-7.7		

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Concomitant medications

Concomitant medications administered were representative of those routinely prescribed for adult patients with FL, treatment and prophylaxis of AEs related to bridging/LD therapy, and treatment of CRS and associated events as recommended by the study protocol.

At the time of the current data cut-off:

- All patients in the Infused set with one exception received non-study concomitant medications
- The most commonly used concomitant medications (in >30% of patients) by ATC class included the below, presented in decreasing order (Study E2202 CSR-Table 14.3-3.1):
    - Anti-infectives for systemic use in 93.8% of patients (primarily Bactrim (42.3%))
    - Alimentary tract and metabolism medications in 79.4% of patients (primarily ondansetron (32.0%))
    - Nervous system medications in 71.1% (primarily paracetamol (53.6%))
    - Blood and blood-forming organs medications in 58.8% (primarily

enoxaparin/enoxaparin sodium (22.7%))
    - Dermatological in 50.5% (primarily acyclovir (27.8%))
    - Musculoskeletal system medications in 50.5% (primarily allopurinol (40.2%))
    - Antineoplastic and immunomodulating agents in 47.4% (primarily filgrastim (25.8%), which was given following the restrictions defined by the Study E2202-Appendix 16.1.1 Protocol Section 6.4
    - Cardiovascular system medications in 37.1% of patients
- 17 patients (17.5%) in the Infused set received anticytokine medication for CRS. All 17 patients received tocilizumab and 4 of them received corticosteroids in addition (Study E2202 CSR-Table 14.3-3.3).

Concomitant medications prior to or after the start of study treatment are listed by patient in Study E2202 CSR-Listing 16.2.5-2.1.

Bridging therapy

Of the 97 patients infused, 44 patients (45.4%) received optional antineoplastic bridging therapy prior to tisagenlecleucel infusion. The most commonly used agents (in ≥ 5% of patients) were rituximab (21.6%), dexamethasone (11.3%), gemcitabine (10.3%), oxaliplatin (7.2%), prednisolone (7.2%), etoposide (6.2%), cyclophosphamide (5.2%), and vincristine (5.2%) (Study E2202 CSR-Table 14.3-2.2). In 5 patients, only corticosteroids were administered as bridging therapy. Furthermore, two patients received bridging radiotherapy – one patient received only radiotherapy and the other patient received radiotherapy and corticosteroids (Study E2202 CSR-Listing 16.2.5-2.2.).

Bridging therapies are listed by patient in Study E2202 CSR-Listing 16.2.5-2.2.

The FDA's Assessment:

Out of 90 subjects included in FDA's primary efficacy analysis, 40 subjects (44%) received bridging therapy. The most commonly used bridging chemotherapy regimens are as follows:

Table 188: FDA Reviewer - Commonly used bridging therapy in subjects included in primary efficacy analysis

Bridging therapy	Number, n (Total N=90)	%
Rituximab	20	22%
Dexamethasone	12	13%
Gemcitabine	11	12%
Prednisolone	10	11%
Oxaliplatin	7	8%
Etoposide	7	8%
Vincristine	5	6%

Ifosfamide	4	4%
Bendamustine	4	4%
Methylprednisolone	4	4%
Cyclophosphamide	4	4%
Cisplatin	3	3%
Idelalisib	3	3%
Obinutuzumab	3	3%

Lymphodepleting chemotherapy

All infused patients received LD chemotherapy prior to tisagenlecleucel infusion. The majority of patients (n = 92) received fludarabine + cyclophosphamide, and the remaining 5 patients received bendamustine (Study E2202 CSR-Table 14.3-2.1).

LD chemotherapy by patient is listed in Study E2202 CSR-Listing 16.2.5-2.2.

Measurement of treatment compliance

Compliance was assured by administration of the study treatment by qualified personnel under the supervision of the Investigator or a deputy and was verified by cellular kinetic determinations. Compliance and drug administration record is provided in Study E2202 CSR-Listing 16.2.5-1.1.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

The study met its primary objective of CRR per IRC at the interim analysis with a data cutoff date of 26-May-2020, when 52 of the 97 infused patients with measurable disease at baseline had either completed 6 months from infusion or had discontinued earlier. The CRR per IRC was 65.4% (99.5% CI: 45.1, 82.4).

Results of the primary analysis, conducted when 94 patients had either completed 6 months of follow-up or had discontinued for any reason (corresponding to a 28-Sep-2020 data cutoff date), confirmed the benefit associated with tisagenlecleucel in the treatment of patients with r/r FL, with high CRR per IRC in the EAS (66.0%).

Results from the extended follow up analysis, corresponding to a 29-Mar-2021 data cutoff date, provide compelling evidence for the efficacy of tisagenlecleucel in the treatment of adult patients with r/r FL, with Study E2202 consistently meeting its primary endpoint at the interim, primary and the extended follow-up analysis. CRR per IRC assessment in the EAS was 69.1% (95% CI: 58.8, 78.3) (Table 19). An additional 16 patients (17.0%) achieved PR. Among 31 patients with an initial PR per IRC assessment, 15 patients converted to CR; for 13 out of these 15 patients, this occurred within 6 months post-tisagenlecleucel infusion (Study E2202 CSR-Section 11.2.1).

Table 199: Applicant - BOR and ORR per IRC assessment (EAS)

	All patients N=94	
	n (%)	**95% CI**
Best overall response		
CR	**65 (69.1)**	**(58.8, 78.3)**
PR	16 (17.0)	
SD	3 (3.2)	
PD	9 (9.6)	
Unknown[1]	1 (1.1)	
Overall response rate (ORR: CR+PR)	**81 (86.2)**	**(77.5, 92.4)**
[1] This patient received a lower dose than the assigned range of CAR-positive viable T cells. The Investigator started a new anticancer treatment before Month 3. - For ORR the 95% exact Clopper-Pearson CIs are displayed. Source: Study E2202 CSR-Table 14.2-1.1		

Sensitivity and supplemental analyses

The robustness and consistency of the primary analysis of CRR (per IRC assessment) was confirmed by the results of multiple predefined sensitivity and supplemental analyses.

CRR per local Investigator assessment

The CRR per local Investigator assessment was 72.3% (95% CI: 62.2, 81.1), which is consistent with the IRC assessment (Table 20). The concordance rate between the IRC and local Investigator assessments with regard to BOR was 86.2% (Study E2202 CSR-Table 14.2-1.4).

Table 20: Applicant – BOR and ORR per local Investigator assessment (EAS)

	All patients N=94	
	n (%)	**95% CI**
Best overall response		
CR	**68 (72.3)**	**(62.2, 81.1)**
PR	17 (18.1)	
SD	3 (3.2)	
PD	6 (6.4)	
Unknown[1]	1 (1.1)	
Overall response rate (ORR: CR+PR)	**85 (90.4)**	**(82.6, 95.5)**
- For ORR the 95% exact Clopper-Pearson CIs are displayed. Source: Study E2202 CSR-Table 14.2-1.5		

CRR using different analysis sets per IRC and local Investigator assessment

Consistent results (with those of the EAS) were observed when CRR was analyzed across different analysis sets (Table 21).

Table 21: Applicant – CRR and ORR per local Investigator and IRC assessment – Enrolled set, Tisagenlecleucel infused set, mEAS, and PPS

	IRC assessment		Local assessment	
	n (%)	95% CI	n (%)	95% CI
CRR				
Enrolled set (N=98)	67 (68.4)	(58.2, 77.4)	70 (71.4)	(61.4, 80.1)
Tisagenlecleucel infused set (N=97)	67 (69.1)	(58.9, 78.1)	70 (72.2)	(62.1, 80.8)
mEAS (N=90)	62 (68.9)	(58.3, 78.2)	65 (72.2)	(61.8, 81.1)
PPS (N=85)	62 (72.9)	(62.2, 82.0)	64 (75.3)	(64.7, 84.0)
ORR				
Enrolled set (N=98)	84 (85.7)	(77.2, 92.0)	88 (89.8)	(82.0, 95.0)
Tisagenlecleucel infused set (N = 97)	84 (86.6)	(78.2, 92.7)	88 (90.7)	(83.1, 95.7)
mEAS (N=90)	77 (85.6)	(76.6, 92.1)	81 (90.0)	(81.9, 95.3)
PPS (N =85)	74 (87.1)	(78.0, 93.4)	78 (91.8)	(83.8, 96.6)
ORR: CR+PR Source: Study E2202 CSR-Table 14.2-1.2, Table 14.2-1.3, Table 14.2-1.5, Table 14.2-1.7				

Subgroup analysis of CRR per IRC assessment

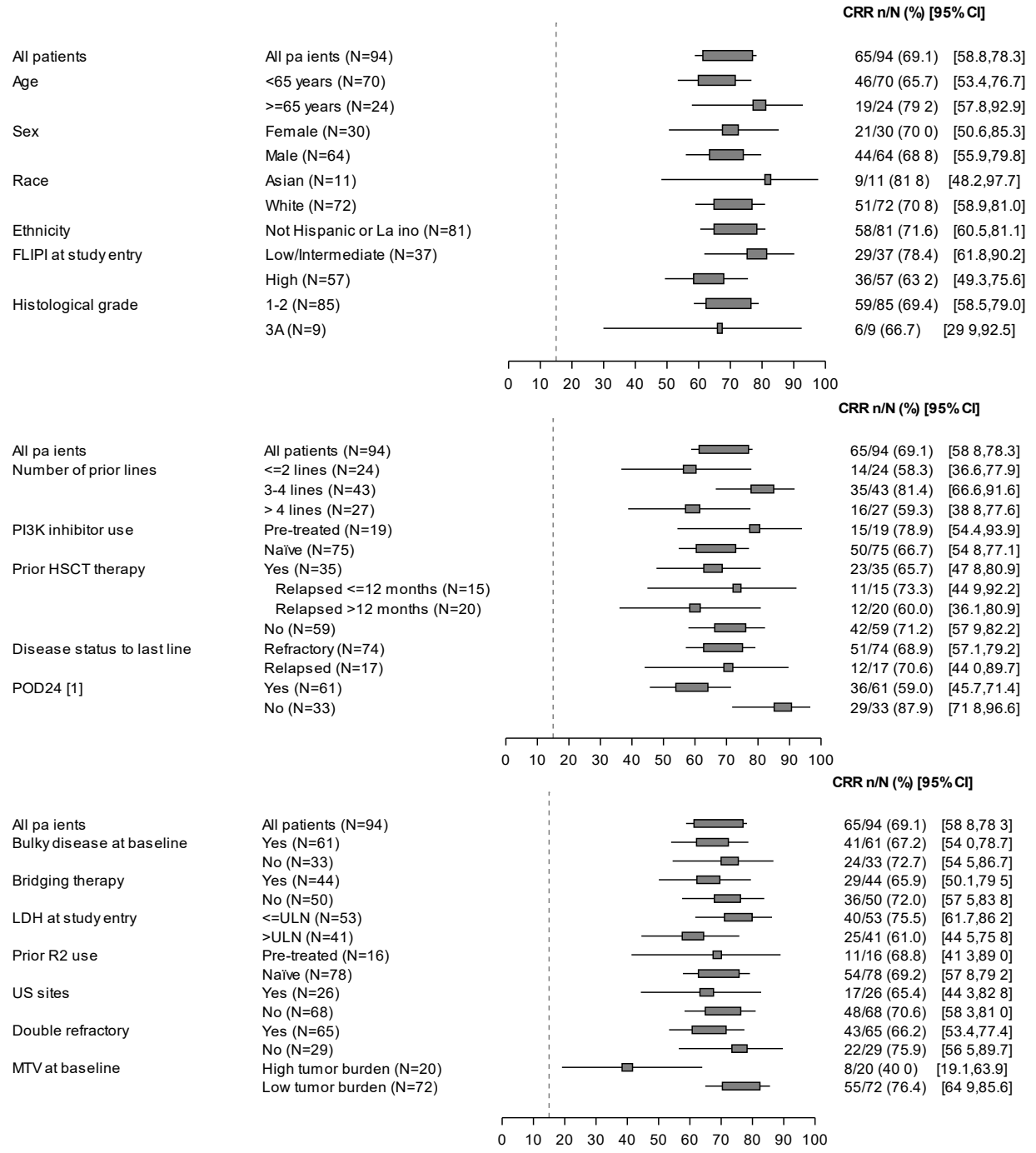
A homogeneous treatment effect was evident across all subgroups (Figure 3), with CRRs ranging from 40.0% to 87.9%. Results were similar to those of the overall study population in the EAS, in particular for the following high-risk subgroups:

- Patients refractory to last line of prior therapy (68.9%)
- Patients with bulky disease at baseline (67.2%)
- Patients who were double refractory (66.2%)
- Patients who received bridging therapy (65.9%)
- Patients with high FLIPI (63.2%) and high LDH (61.0%)
    - Patients belonging to POD24 group (59.0%)

Patients with high TMTV showed a decreased CRR (40.0%), although in this subgroup the ORR was less impacted (75%) (Study E2202 CSR-Table 14.2-1.1p). These estimates should be interpreted with caution given the small number of patients (N=20). The TMTV is a quantitative tumor burden parameter, obtained from FDG-PET/CT. A TMTV value >510 cm3 was used as threshold to define high TMTV (Delfau-Larue MH et al 2018).

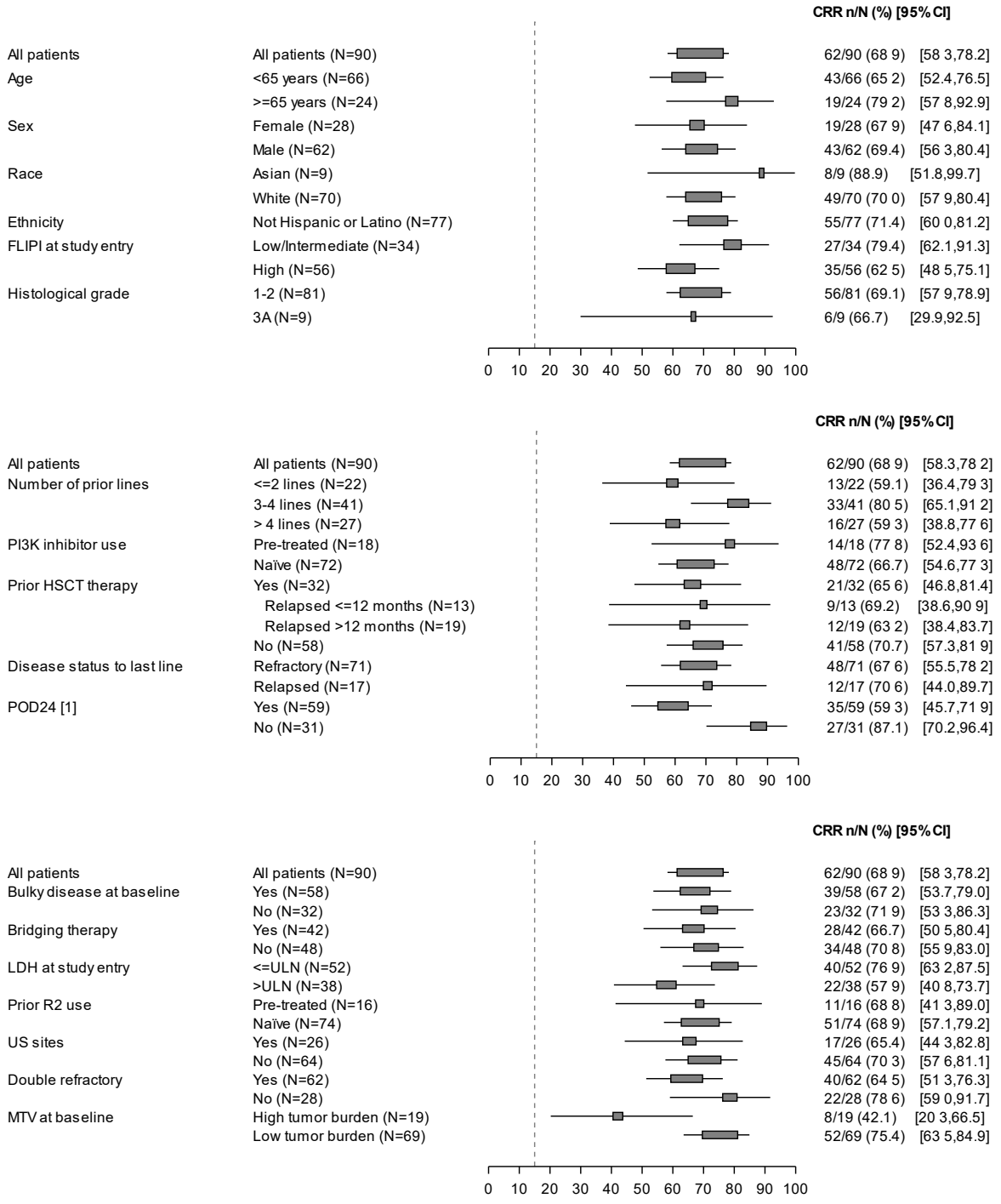
Similar results were seen in the subgroup analysis with the mEAS (Figure 3).

Figure 3: Applicant – CRR treatment effect per IRC assessment – Forest plot for subgroups (EAS)



The 95% CIs are exact Clopper-Pearson CIs calculated for each subgroup.
Source: Study E2202 CSR-Figure 14.2-1.1

Figure 4: Applicant – CRR treatment effect per IRC assessment – Forest plot for subgroups (mEAS)



The 95% CIs are exact Clopper-Pearson CIs calculated for each subgroup.
Source: Study E2202 CSR-Figure 14.2-1.5

The FDA's Assessment:

The primary objective of E2202 Study was to evaluate the efficacy of tisagenlecleucel in adults with r/r FL after two or more lines of systemic therapy by measuring primary end point of CRR as assessed by Independent Review Committee (IRC) using the 2014 Lugano Classification. Baseline disease and the disease response at prespecified time points were performed by the site investigator and by the IRC.
The central imaging review was performed by independent radiologist at (b) (4) international, which was responsible for monitoring compliance with study documents governing the acquisition of study images, controlling, and monitoring the flow of images from the investigative sites into the CRO, conducting the image analysis, and ultimately providing a data export to the applicant.

FDA's primary efficacy evaluation was based upon response rates and duration of response in 90 consecutively treated subjects with r/r FL with measurable disease at baseline at determined by IRC and have had at least 9 months of follow up from first objective response in the responders unless discontinued earlier. As agreed during the preBLA meeting, one subject had less than 9 months of follow up from first response since the subject missed Month 3 evaluation due to COVID-19 Pandemic.

Table 22: FDA Reviewer – Change in response after FDA review and adjudication

Subject	Comment	Outcome	Applicant's response
(b) (6)	CR at Eval 2 on (b) (6) was downgraded to PR, since 1) Bone marrow on (b) (6) to confirm the radiologic CR was done after 28 days window, 2) the subsequent evaluation a month later on (b) (6) showed progression of disease.	BOR changed from CR to PR	Agreed by the Applicant
	Partial Response (PR) at Eval 2 on (b) (6) was downgraded to Progressive Disease (PD), since per IRC review (ADEFIRC_AD data), there is a 'new recurrent FDG uptake' in the marrow on PET CT done on (b) (6). Per Lugano Criteria 2014, new or	BOR of PR unchanged since the subject had PR at Eval 1. Adjustment was made to the DOR calculation.	The applicant provided explanation that the IRC reviewer considered, the FDG uptake was treatment-related rather than being lymphoma-related.

	recurrent FDG avid foci in bone marrow should be a PD.		

Table 23: FDA Reviewer – Subjects with one or more missing response assessment

Subject ID	Applicant's response to FDA's query
(b) (6)	The subject achieved BOR of CR by IRC at Month 3 and had their last assessment at Month 6 ((b) (6)) showing ongoing CR by IRC. On Day 277 ((b) (6)), before their Month 9 assessment, the subject was infected by COVID-19, was then discontinued from the trial due to Investigator's decision and enrolled to a COVID-19 investigational treatment trial.
	The subject achieved BOR of CR by IRC at Month 3 and had their last assessment at Month 6 on (b) (6) showing ongoing CR by IRC. The patient then missed their Month 9 assessment (planned in Dec 2020 per protocol) and subsequently was declared lost to follow-up on 11-Mar-2021.
	The subject achieved BOR of PR per IRC at Month 3 and had their last assessment at Month 6 ((b) (6)). Response from the Month 6 visit was assessed by IRC as a PR. However local review determined the patient to have PD at Month 6, thus the subject discontinued efficacy assessments as per protocol.
	The subject had a BOR of Unknown per IRC before Month 3, then the subject started new anticancer therapy on (b) (6) before Month 3 assessment, therefore Month 3 assessment was not included in the efficacy analysis.

Table 244: FDA Reviewer –Response Rates in Subjects with Relapsed or Refractory FL

Response	Primary Efficacy Population N=90	All Leukapheresed patients N=98
Overall response rate (ORR=CR+PR), n (%) (95% CI)	77 (86%) (76.6, 92.1)	84 (86%) (77.2, 92.0)
Complete response (CR), n (%) (95% CI)	61 (68%) (57.1, 77.2)	66 (67%) (57.1, 76.5)
Partial response (PR), n (%) (95% CI)	16 (17.8%) (10.5, 27.3)	66 (67%) (57.1, 76.5)

Stable disease (SD), n (%) (95% CI)	3 (3.2%) (0.01, 0.09)	66 (67%) (57.1, 76.5)
Progressive disease (PD), n (%) (95% CI)	9 (9.6%) (0.05, 0.18)	66 (67%) (57.1, 76.5)
Unknown BOR, n (%) (95% CI)	1 (1.1%) (0.00, 0.06)	66 (67%) (57.1, 76.5)
Source: FDA's primary review of ADRS, ADTTEITC, ADTR, ADB2A, ADB2B datasets, and Case Study Report Table 11-3, FDA statistical reviewer's memo *Two patients, included in the Primary Efficacy Population, with best overall response of CR, had their disease relapsed more than 6 months after the last line of therapy.		

Data Quality and Integrity

The Applicant's Position:

This extended follow-up analysis presents data collected up to the data cutoff date of 29-Mar-2021, when at least 90 patients were infused with tisagenlecleucel and had completed 12 months follow up from infusion, or discontinued earlier. The database was locked on 07-May-2021 after all the necessary actions had been completed and the database had been declared to be complete and accurate.

The FDA's Assessment:

The data submitted with the data cutoff date of March 29, 2021 included data on 98 enrolled/leukapheresed (intention to treat) subjects. Out of those 98 subjects, one subject did not receive the manufactured product since they had achieved a complete response to previously administered antineoplastic therapy. Primary efficacy analysis was performed on first 90 consecutively treated subjects with r/r FL with measurable disease at baseline per IRC and had at least 9 months of follow up from the date of first objective response (PR or CR) or discontinued earlier, except for one subject with <9 month of such follow up since they missed 3-month disease assessment due to COVID 19 Pandemic. Of note, the initial data submitted had key deficiencies such as lack of key flags, date of assessments etc. The applicant subsequently submitted revised datasets, which caused delay in review process, and triggered major amendment.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Overall response rate

The ORR per IRC assessment was 86.2% (81 patients; 95% CI: 77.5, 92.4) and per local Investigator assessment was 90.4% (85 patients; 95% CI: 82.6, 95.5), demonstrating consistency in the results (Table 9 and Table 10).

Among 31 patients with initial PR per IRC assessment, 15 patients converted to CR (i.e., achieved BOR of CR) which occurred within approximately 6 months post-tisagenlecleucel infusion for the majority of these 15 patients (Study E2202 CSR-Figure 14.2-1.2).

The ORR results of this extended follow-up analysis were consistent with both the interim (82.7%) and primary analyses (86.2%).

Sensitivity and supplemental analyses

The ORR results were driven by high CRRs, and the robustness of the ORR per IRC was confirmed by the results of predefined sensitivity and supplemental analyses using the mEAS (85.6%), PPS (87.1%), and Tisagenlecleucel infused set (86.6%) (Table 11).

Subgroup analysis

Across the various subgroup analyses, the ORR per IRC ranged from 75.0% to 94.6% (Study E2202 CSR-Figure 14.2-1.3).

A homogeneous treatment effect was observed. Furthermore, the ORR was consistent across the high-risk subgroups (mentioned earlier) and was > 80% in all these subgroups.

Similar results were seen in the subgroup analysis with the mEAS (Study E2202 CSR-Figure 14.2-1.6).

Duration of response

The median DOR per IRC was not reached as of the 29-Mar-2021 data cut-off date.

Responses (CR or PR) per IRC were achieved in 81 patients, with the estimated probability of remaining in response for 9 months being 76.0% (95% CI: 64.6, 84.2) (Table 25).

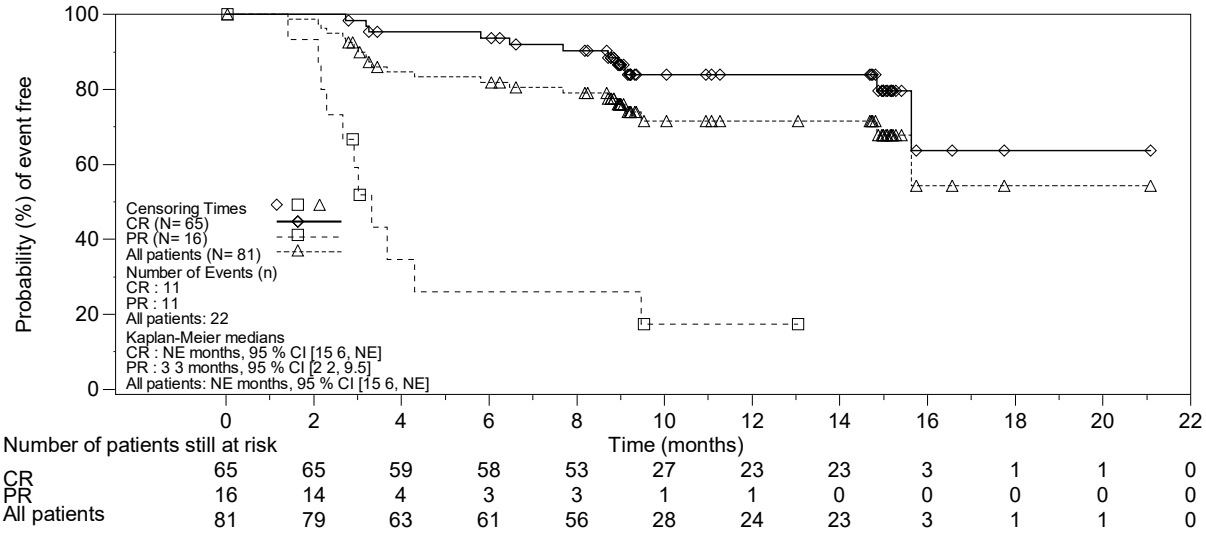
The estimated probability of remaining in response for patients achieving CR was 86.5% at Month 9 vs 25.9% for patients achieving PR as BOR (Study E2202 CSR-Table 14.2-2.4); the median DOR for patients achieving PR was 3.3 months (Figure 4). These results demonstrate that CR translates to prolonged DOR, when compared to the DOR of patients achieving only PR as BOR.

Table 25: Applicant – DOR per IRC and local Investigator assessment (EAS)

Responders: Patients with BOR of CR or PR		
	All patients N=94	
	IRC assessment	**Local assessment**
Events/Responders (%)	22/81 (27.2)	24/85 (28.2)
Percentiles (95% CI)[1]		
25th	9.1 (3.7, NE)	8.9 (3.3, 15.6)
50th	NE (15.6, NE)	15.6 (15.3, NE)
75th	NE	NE (15.6, NE)
% Event-free probability estimates (95% CI)[2]		
Month 3	91.2 (82.5, 95.7)	91.5 (83.1, 95.9)
Month 6	82.0 (71.4, 88.9)	79.2 (68.7, 86.5)
Month 9	76.0 (64.6, 84.2)	74.8 (63.6, 83.0)
Month 12	71.6 (58.9, 80.9)	72.9 (61.3, 81.5)
Month 15	67.8 (53.4, 78.6)	70.1 (57.4, 79.6)

[1]Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
Source: Study E2202 CSR-Table 14.2-2.1

Figure 5: Applicant – Kaplan-Meier plot of DOR by BOR per IRC assessment (EAS)



Duration of response results per local Investigator assessment were consistent with the IRC assessment (Table 25). Furthermore, DOR in mEAS is presented in Table 26; the results were consistent with the EAS.

Table 26: Applicant – DOR per IRC assessment (mEAS)

Responders: Patients with BOR of CR or PR	
	All patients N=90
Events/Responders (%)	21/77 (27.3)
Percentiles median (95% CI)[1]	NE (15.6, NE)
% Event-free probability estimates (95% CI)[2]	
Month 3	92.1 (83.2, 96.4)
Month 6	82.4 (71.6, 89.4)
Month 9	76.4 (64.7, 84.6)
Month 12	71.9 (59.0, 81.3)
Month 15	68.1 (53.5, 79.0)

[1]Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
Source: Study E2202 CSR-Table 14.2-2.3

Progression-free survival

The estimated progression-free probability was 67.0% (95% CI: 56.0, 75.8) at Month 12 per IRC assessment. The median PFS per IRC was 18.4 months; however, this should be interpreted with caution since there were limited numbers of patients still at risk after Month 18 (Study E2202 CSR-Table 14.2-3.1, Figure 14.2-3.1).

Of note, as only 3 patients had best overall response of SD and none of them had PFS longer than 6 months (one progressed, one started a new therapy, and one withdrew consent), PFS estimates beyond 6 months cannot be biased by the natural history of disease (e.g., slow-growing tumor). In this study PFS is driven by durable responders and can be interpreted as estimated proportion of patients with PR or CR at given timepoint.

Computing PFS from enrollment in the Enrolled set, median PFS was not reached, and the estimated progression-free probability was 71.6% (95% CI: 61.1, 79.7) at Month 12 (Study E2202 CSR-Table 14.2-3.2).

Median PFS per IRC was 18.4 months (95% CI: 12.3, NE) in the mEAS; however, this should be interpreted with caution since there were limited numbers of patients remaining at risk after Month 18. The estimated event-free probability was 68.0% (95% CI: 56.8, 76.8) at Month 12.

Overall survival

The median OS was not reached at the time of the 29-Mar-2021 data cutoff date. Seven deaths occurred during the study.

In the EAS, the estimated probability of survival was 95.3% (95% CI: 88.0, 98.2) at Month 12 and 91.6% (95% CI: 81.7, 96.2) at Month 18.

Median OS was not reached in the mEAS at the time of the data cutoff. The estimated probability of survival was 96.4% (95% CI: 89.1, 98.8) at Month 12 and 92.6% (95% CI: 82.6, 96.9) at Month 18. OS was also analyzed in the Enrolled set (from enrollment) and the Tisagenlecleucel infused set, and yielded similar results [Study E2202 CSR-Table 14.2-4.1, Table 14.2-4.3).

The FDA's Assessment:

The following sections on the duration of response, overall survival and progression-free survival were extracted from FDA's statistical reviewer's memo.

There was no formal hypothesis testing planned for the below secondary endpoints. Analysis of these secondary endpoints were conducted by FDA statistical reviewer based on updated datasets submitted on December 15, 2021.

Overall response Rate

The ORR was 85.6% (77 patients, 95% CI: 76.6, 92.1) per IRC assessment and 90.0% (81 patients, 95% CI: 81.9, 95.3) per local Investigator assessment in mEAS (Table 18, 19 and 20). The ORR results of this extended follow-up analysis were consistent with the results of the interim (ORR=82.7% with data cut-off date: 26-May-2020) and the primary analyses (ORR=86.2% with data cut-off date September 28, 2020) of study E2202.

Duration of response (DOR)

DOR was calculated for the 77 patients who achieved CR or PR per IRC review in mEAC. The median DOR was not reached. The probability of remaining in response at 9 months and 12 months were 74.9% (95% CI: 63.5, 83.3) and 70.5% (95% CI: 57.9, 80.0), respectively. Table 27 summarizes the DOR results for mEAS based on IRC assessment and local Investigator assessment. The KM plot of DOR per IRC assessment is presented in Figure 2.

Table 27: FDA Reviewer/Statistical Reviewer - DOR results per IRC and local Investigator assessment (mEAS)

All patients, N=90 (mEAS)		
	Patients with BOR of CR or PR	
	IRC assessment	local Investigator assessment

Events/Responders (%)	22/77	23/81 (28.4)
Percentiles (95% CI)		
25th	9.1 (3.3, 15.6)	9.1 (3.3, 15.6)
50th	NE (15.6, NE)	15.6 (15.3, NE)
75th	NE (NE, NE)	NE (15.6, NE)
% Event-free probability estimates (95% CI)		
Month 3	92.1 (83.2, 96.4)	92.4 (83.8, 96.5)
Month 6	81.1 (70.2, 88.4)	79.4 (68.6, 86.9)
Month 9	75.2 (63.5, 83.6)	75.1 (63.7, 83.3)
Month 12	70.8 (58.0, 80.3)	73.1 (61.3, 81.9)
Month 15	67.1 (52.6, 78.0)	70.3 (57.5, 79.9)

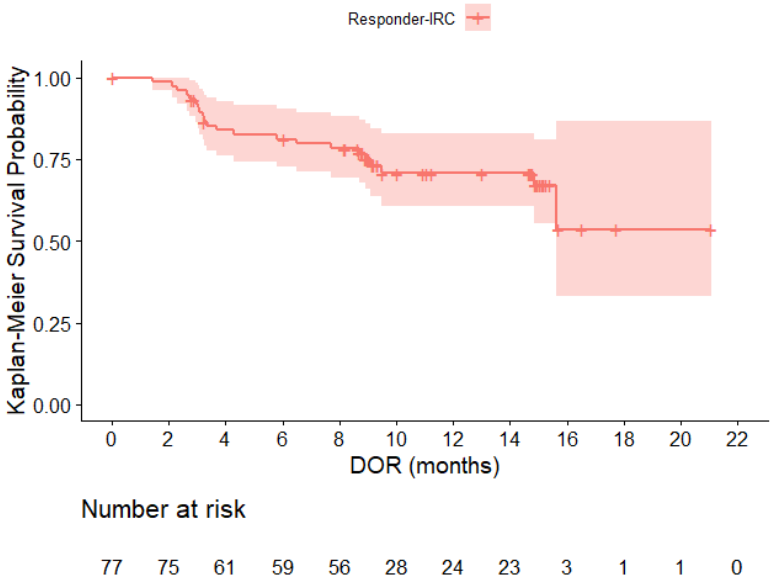
(Source: reviewer's analysis of DOR)

The FDA's Assessment:

Since the nature of FL is indolent, the event-free probability was assessed across time points to assess durability of response. Event-free probability is the estimated probability that a patient will remain event free, i.e. the probability of remaining in continued response, up-to a specified time point. The event-free probability was obtained from KM survival estimates.

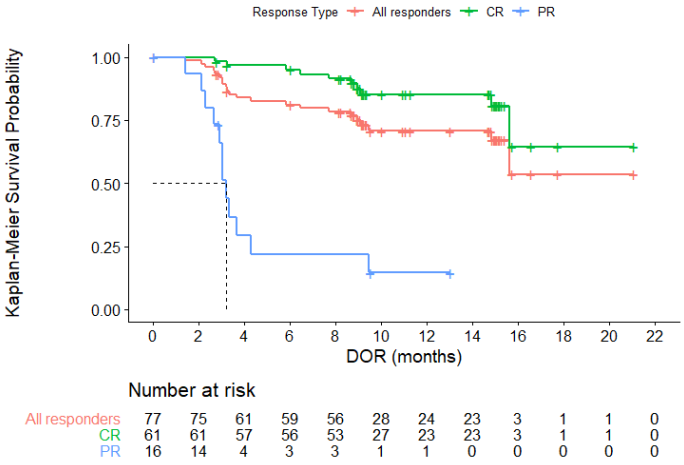
KM estimate for DOR is shown in Figure 6 and the KM curves of DOR by best response achieved per IRC assessment is presented in Figure 7. Duration of response for subjects with best response of CR appears to be longer compared to that for PR, although the group of CR did not reach its median DOR at the time of clinical cut off.

Figure 6: FDA - Kaplan-Meier curves of DOR for responders (CR or PR) per IRC in mEAS



(Source: FDA statistical reviewer's analysis)

Figure 7: FDA - Kaplan-Meier curves of DOR by BOR per IRC assessment (mEAS)



(Source: FDA statistical reviewer's analysis)

Progression-free Survival (PFS)

Table 28 summarizes the PFS results for mEAS based on IRC and local investigator assessment, respectively. There were 33 PFS events (disease progression or death) in total per IRC. The estimated 12-month progression-free survival probability was 67.0% (95% CI: 55.8, 75.9) per IRC. The median PFS per IRC was 18.4 months (95% CI: 12.3, NE) with a lower limit of the 95% confidence limits at 12.3 months and an upper limit

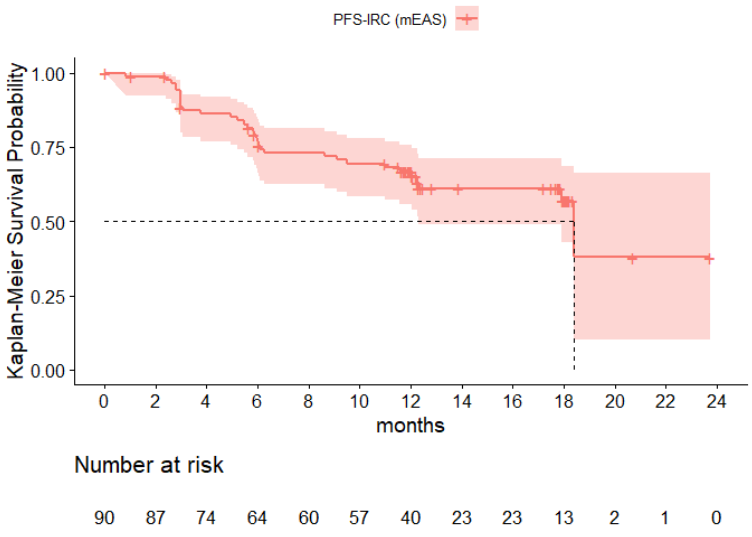
unattainable. The KM plot of PFS per IRC assessment is presented in Figure 8 and the KM plot of PFS by best response achieved is presented in Figure 9.

Table 28: FDA Reviewer/Statistical Reviewer - PFS results in mEAS

All patients, N=90 (mEAS)		
	IRC assessment	local Investigator assessment
Events/Responders (%)	33/90 (36.7)	32/90 (35.6)
Percentiles (95% CI)	(26.8, 47.5)	(25.7, 46.3)
25th	6.1 (5.2, 12.1)	6.2 (5.7, 12.3)
50th	18.4 (12.3, NE)	18.4 (15.6, NE)
75th	NE (18.4, NE)	NE (18.4, NE)
% Event-free probability estimates (95% CI)		
Month 3	88.5 (79.7, 93.7)	90.8 (82.5, 95.3)
Month 6	76.8 (66.3, 84.4)	78.1 (67.9, 85.5)
Month 9	71.9 (61.1, 80.2)	73.4 (62.8, 81.5)
Month 12	67.0 (55.8, 75.9)	68.6 (57.6, 77.3)
Month 15	61.1 (49.0, 71.2)	64.9 (53.2, 74.3)
Month 18	57.0 (43.1, 68.8)	62.3 (49.9, 72.4)

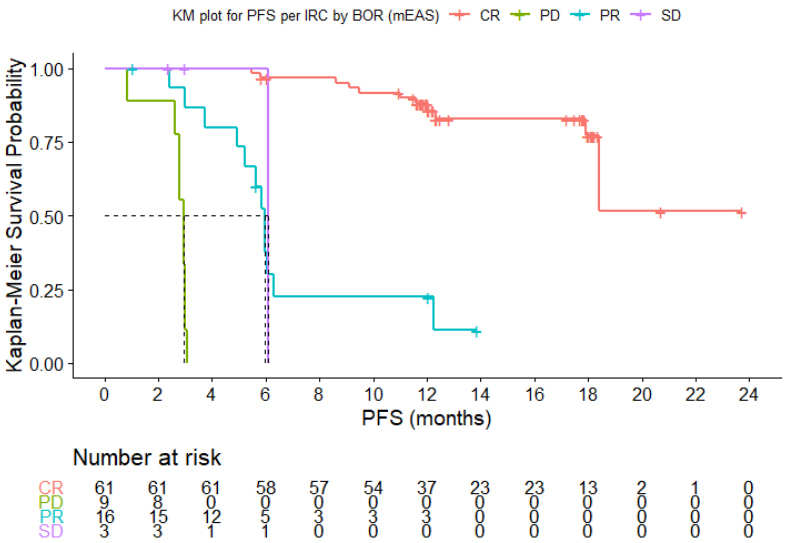
(Source: FDA statistical reviewer's analysis)

Figure 8: FDA - Kaplan-Meier Curves of PFS per IRC for mEAS



The KM plot of PFS by best response achieved (i.e., complete, response, partial response, progressive disease, and stable disease) per IRC assessment is presented in Figure 9. There's one subject (subject ID: (b) (6)) whose overall best response status is unknown.

Figure 9: FDA - Kaplan-Meier Curves of PFS per IRC by BOR for mEAS



(Source: FDA statistical reviewer's analysis)

Overall Survival (OS)

The median OS was not reached at the time of the data cut-off date. Six deaths had occurred in the study for subjects in the mEAS. the estimated probability of survival was 96.4% (95% CI: 89.1, 98.8) at Month 12 and 92.6% (95% CI:82.6, 96.9) at Month 18. The OS results are shown in table 29 and the overall K-M curves are shown in Figure 10.

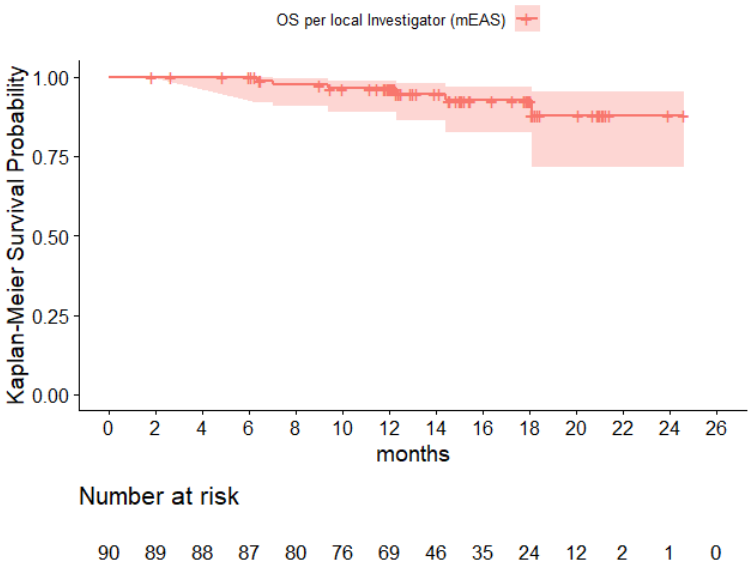
Table 29: FDA Reviewer/Statistical Reviewer - OS results in mEAS

	mEAS, N=90
Events/Responders (%)	6/90 (6.7)
Percentiles (95% CI)	
25th	NE (18.1, NE)
50th	NE
75th	NE
% Event-free probability estimates (95% CI)	
Month 3	100
Month 6	100
Month 9	97.7 (90.7, 99.4)
Month 12	96.4 (89.1, 98.8)

Month 15	92.6 (82.6, 96.9)
Month 18	92.6 (82.6, 96.9)

(Source: Table 14 on page 33, section 4.3.6 of Updated Efficacy; reviewer's analysis)

Figure 10: FDA - Kaplan-Meier Curves for Overall Survival (mEAS)



(Source: FDA statistical reviewer's analysis)

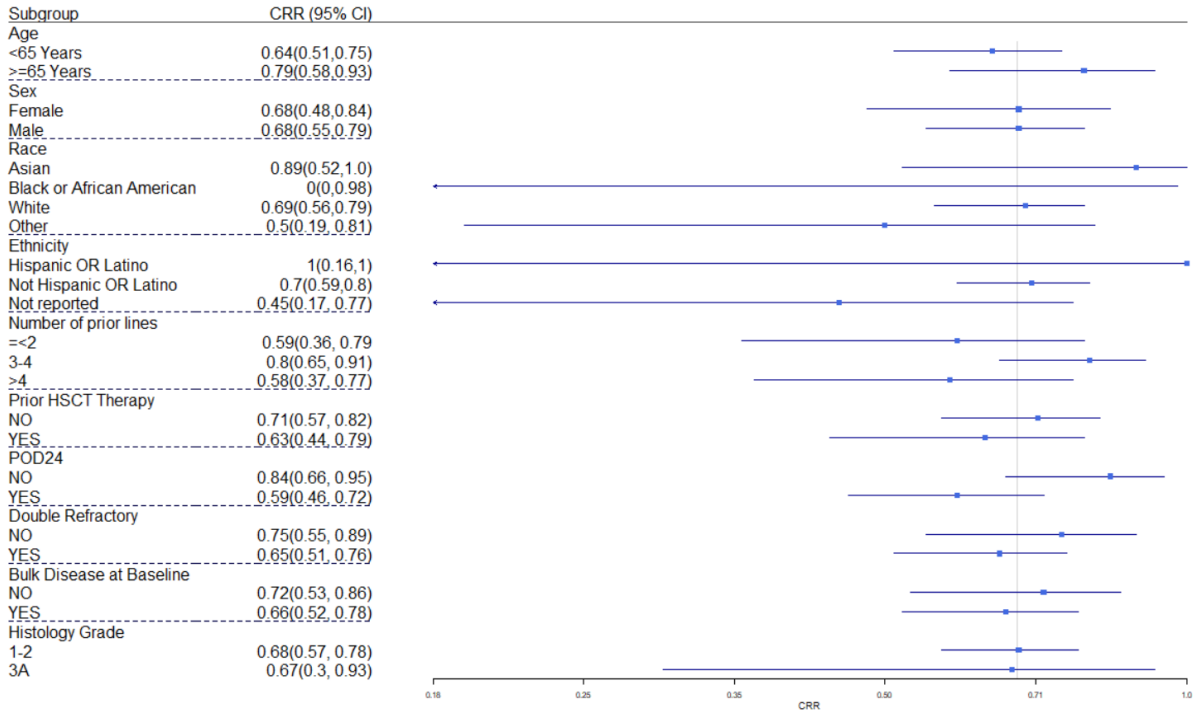
The FDA's Assessment:

The study E2202 is a single-arm study with no comparator group; hence, time-to-event endpoint (such as PFS, OS) data are not interpretable. Therefore, the PFS and OS data have limited value in benefit risk assessment, and should be interpreted with caution.

Subpopulation Analyses

Figure 11 shows the forest plot of CRR per IRC assessment in mEAS across baseline characteristic subgroups by age, sex, race and other baseline factors. Robustness of CRR was further confirmed by a series of predefined sensitivity analyses, with CRRs ranging from 59% to 66% across different high-risk subgroups, i.e., patients who were double refractory, patients with high FLIPI, bulky disease at baseline and patients belonging to POD24 group. The lower limit of 95% exact Clopper-Pearson confidence interval for CRR is above the null hypothesis rate of 15% for each subgroup.

Figure 11: FDA - Forest plot of CRR per IRC by subgroup (mEAS)



(Source: FDA statistical reviewer's analysis)

Quality of life

Patient-reported outcomes data are available from patients who completed the required questionnaire.

FACT-LYM and SF-36 questionnaires

The FACT Lym scores showed improvement in QoL from baseline in the early months post infusion (Month 3 and Month 6), and a stabilization over time afterwards. Similar results were observed in SF-36 questionnaire results (Study E2202 CSR-Figure 14.2-6.1).

EQ-5D-3L questionnaire

At Month 12, the EQ-5D-3L scores were similar to baseline, without any deterioration (Study E2202 CSR-Figure 14.2-6.2).

EQ-VAS score

The mean EQ-VAS score was 69.4 a t baseline, which increased to 72.9 at Month 6, and 75.2 at Month 12, indicating an overall improvement in health-related QOL after tisagenlecleucel infusion (Study E2202 CSR-Table 14.2-6.2).

Overall, the PRO scores show initial improvement in early months and then stabilization of the QoL afterwards.

The FDA's Assessment:

Patient Reported Outcomes (PRO) data was submitted with this sBLA application. However, because of the single-arm design of the trial with no comparator, the PRO data is considered descriptive and is not considered for inclusion in the labeling.

Dose/Dose Response

The Applicant's Position:

Considering the positive benefit risk ratio and lack of dose-related safety concerns in this patient population, the dose range of 0.6 to 6.0×10^8 CAR-positive viable cells, consistent with approved dose range in DLBCL patients, is recommended in r/r FL patients.

- Dose-response and dose-exposure: Across the dose range studied, dose and exposure were not correlated. Additionally, favorable clinical responses were observed across the proposed dose range of 0.6 to 6.0×10^8 CAR-positive viable T cells.
- Dose-safety: The probability of any grade serious neurologic events and time to resolution of cytopenias were not impacted by dose. Lower incidence of grade 1 or 2 CRS was observed (32%) at the lowest dose quartile ($\leq1.4\times10^8$) compared to ~54% at all other dose quartiles and no high-grade CRS (grade 3 or higher) was observed in Study E2202 across the entire studied dose range within 8 weeks of infusion. Moreover, CRS was manageable in the study with the steps outlined in the CRS algorithm.

Based on the totality of the dose-safety, dose-efficacy, dose-exposure and exposure-response, analyses and considering the positive benefit risk observed across the wide range of doses, the recommended dose range for adult patients with r/r FL is 0.6 to 6.0×10^8 CAR-positive viable T cells, consistent with the approved dose range forKymriah in r/r DLBCL patients. Details are discussed in (Summary of Clinical Pharmacology-Section Section 2.6 and Section 2.7).

The FDA's Assessment:

As discussed in previous sections, the dose used in study E2202 was extrapolated from the approved dose of tisagenlecleucel for the treatment of adult patients with DLBCL. Favorable clinical benefits were observed across the recommended dose without correlation of dose and exposure. Similarly, safety profile remained consistent across the dose range studied.

Durability of Response

The Applicant's Position:

Durability of response is discussed under results of secondary efficacy endpoints above.

The FDA's Assessment:

All responders achieved their response (CR or PR) at the first performed disease response assessment. Of the 30 subjects who initially achieved a PR, 14 subjects (47%) converted to a CR, including 10 subjects at the next subsequent visit and within 6 months post infusion. At median follow up from first objective response of 9.1 months, the median duration of response was non estimable (95% CI 15.6, NE).

Persistence of Effect

The Applicant's Position:

Study E2202 demonstrated sustained efficacy and durable remissions with median follow-ups of ~16 months. This indicates durable antitumor efficacy.

In the EA, at 12 months, 65 patients had a sustained CR and 15 patients had an initial PR converted to CR within approximately 6 months. Responses (CR or PR) per IRC were achieved in 81 patients, with the estimated probability of remaining in response for 9 months being 76.0% (95% CI: 64.6, 84.2). A total of 34 PFS events (disease progression or death) were observed. The estimated progression-free probability was 67.0% (95% CI: 56.0, 75.8) at Month 12. Out of the 97 patients who received a tisagenlecleucel infusion, 7 patients (7.2%) died after infusion. The median OS was not reached, with 12-month OS rate of 95.3% (95% CI: 88.0, 98.2).

The FDA's Assessment:
In the efficacy analysis set of 90 subjects, 77 subjects (86%) achieved overall response of either CR or PR. The estimated event-free probability at 12 months among subjects with BOR of CR (85%; 95% CI 72.2, 92.4) was longer compared to that amongst all responders (71%, 91% CI 58.0, 80.3).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Patient reported outcomes are discussed under results of secondary efficacy endpoints above.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Time to new antineoplastic therapy

The median time to start a new anti-lymphoma therapy was not reached (Study E2202 CSR-Figure 14.2-8.1). Eighteen out of 94 patients in the EAS (18.1%) started new anti-lymphoma therapies after being infused with tisagenlecleucel, which includes medications, allogeneic HSCT, and radiotherapy. The estimated probability of continuing without starting a new anti-lymphoma therapy was 81.9% (95% CI: 72.0, 88.5) at Month 12 and 75.3% (95% CI: 62.9, 84.0) at Month 18 (Study E2202-Table 14.2-8.1). Of note, the two patients who underwent allogeneic HSCT, had received another anti neoplastic therapy prior to the transplant (Study E2202 CSR-Section 11.2.4.2, Listing 16.2.5-4.1, Listing 16.2.6-1.2).

8.1.2. Study A2101J

The Applicant's Description:

This pilot Phase IIa study was designed and conducted by the University of Pennsylvania for patients with r/r CD19+ DLBCL or FL. Data hereby reported from this study are derived from publications only (Schuster et al 2017, Chong et al 2021) and from the related protocol included in the appendix of the first publication. Of note, Novartis has no access to patient-level data for this trial.

Key inclusion criteria were: patients with CD19+ DLBCL or FL with no curative treatment options, a partial response to or stable disease after their most recent therapy and limited prognosis (< 2 years of anticipated survival). Patients with FL were eligible if they had measurable progression of disease less than 2 years after second line immunochemotherapy (excluding single-agent monoclonal antibody therapy).

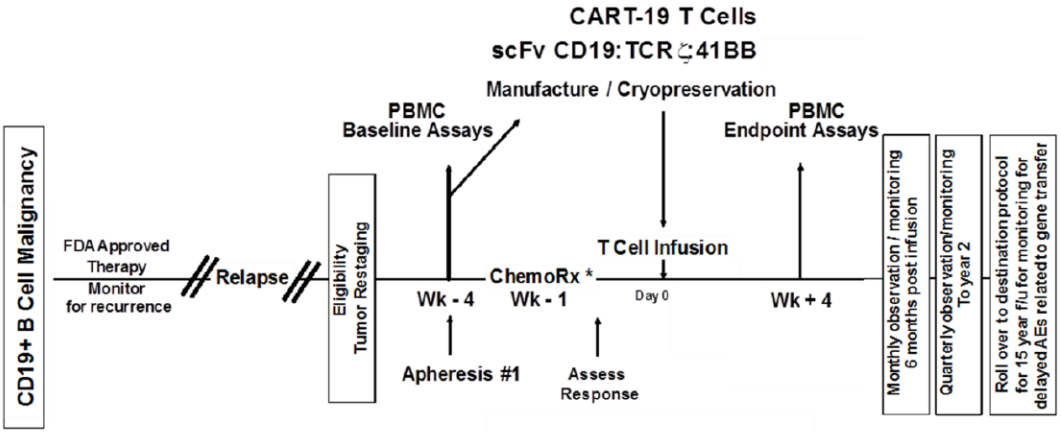
Enrolled patients received tisagenlecleucel infusions between 11-Mar-2014 and 02-Aug-2016; clinical outcome data were reported for 5 years follow-up. The dose, as specified in the protocol, was 1.0 to 5.0 × 10^8 CAR-positive viable T cells (Schuster et al 2017).

The primary objective was to estimate the efficacy of CART-19 cells in NHL patients by measuring ORR at 3 months for all patients receiving the protocol-specified dose of tisagenlecleucel cells. Responses were evaluated using the 1999 International Working Group criteria, with complete responses confirmed on ^{18}F-fluorodeoxyglucose–positron-emission tomography.

Patients had assessment for tumor response every month post-infusion for the first three months and every 3 months for two years. The results were analyzed at 28 months (Schuster et al 2017) and again at 5 years (Chong et al 2021).

The study design is presented in Figure 12.

Figure 12: Applicant – Study A2101J design



Source: Schuster et al 2017

Study population

A total of 49 patients were enrolled in the study, and 38 patients received treatment as specified in the protocol (24 patients with DLBCL and 14 patients with FL). Eleven patients did not receive treatment owing to rapid disease progression with clinical deterioration (5 patients: 4 with DLBCL and 1 with FL), an insufficient T-cell count for the manufacture of tisagenlecleucel cells (5 patients), and withdrawal of consent (1 patient, with DLBCL) (Chong et al 2021). T-cell manufacturing was unsuccessful for 5 patients, all of whom had absolute lymphocyte counts of ≤ 300 /mm^3 (3 had poor T-cell growth, and 2 did not undergo apheresis owing to the degree of lymphopenia).

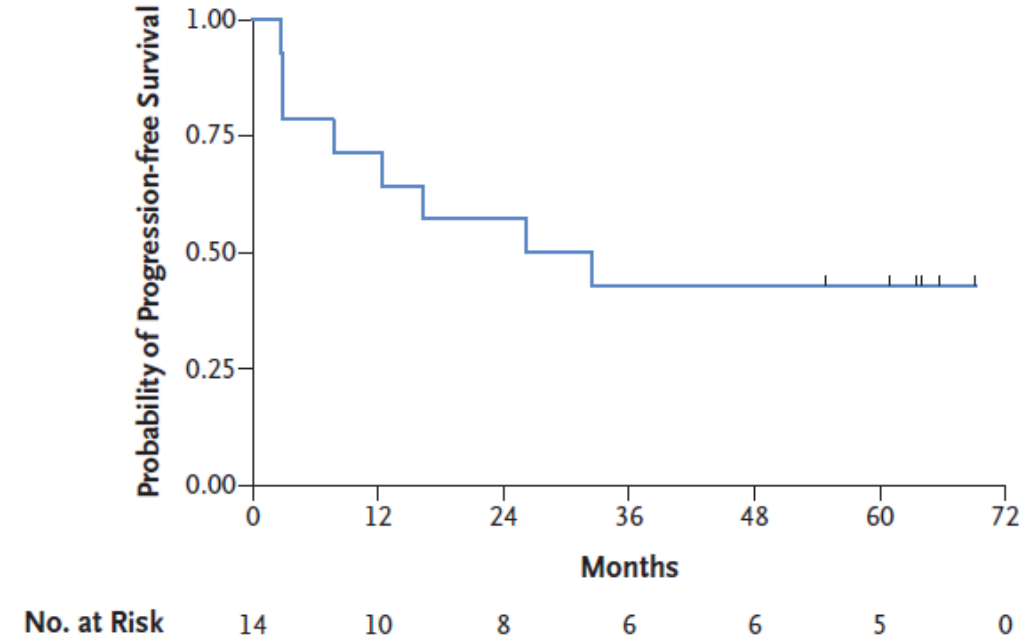
Among the 14 patients with FL, 8 (57%) were double-refractory (defined as progressive disease within 6 months after the last dose of rituximab and the last dose of an alkylating agent) and the median number of prior therapies was 5 (range 2-10) (Schuster et al 2017).

Efficacy results

At 3 months, 11 of 14 patients with FL had a response (79%; 95% CI: 49, 95), and at 6 months, 10 of 14 patients with FL had a CR (71%; 95% CI: 42, 92). Three patients who had a PR at 3 months had a CR by 6 months; 1 patient was in continuous PR at 6 months and experienced PD at 1 year. Median PFS was not reached. Overall, 70% of patients with FL (95% CI: 38 to 88) were progression-free and 89% of patients with FL who had a response (95% CI: 43, 98) had maintained the response at a median follow-up of 28.6 months (Shuster et al 2017).

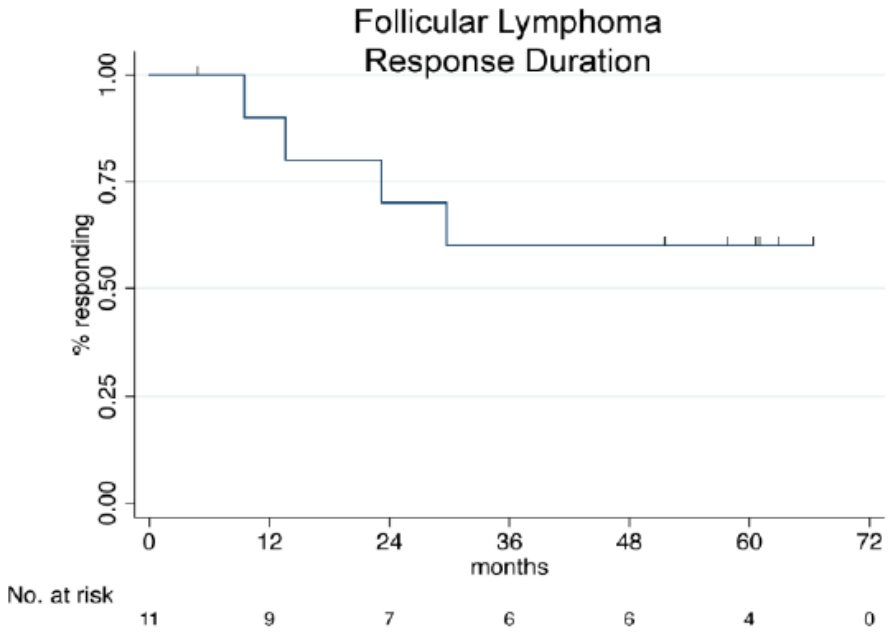
After a median follow-up of 60.7 months, the PFS rate at 5 years was 43% (95% CI: 18, 66) (Figure 13) and median DOR was not reached (Figure 14). The probability of remaining in response 5 years was 60% (Chong et al 2021).

Figure 13: Applicant – Five-year PFS in patients with FL



Source: Adapted from Chong et al 2021

Figure 14: Applicant – Five-year DOR in patients with FL



Source: Adapted from Chong et al 2021

The FDA's Assessment:

As described above, Study A2101J was a pilot Phase IIa study conducted by the University of Pennsylvania for patients with r/r CD19+ DLBCL or FL. The results of the study were previously published (Schuster et al 2017, Chong et al 2021). No patient level data were submitted along with this supplemental BLA application. Therefore, the efficacy review did not involve of review of A2101J data.

8.1.3. Integrated Review of Effectiveness

The efficacy of tisagenlecleucel to support the treatment of adult patients with r/r FL after two or more lines of therapy is based primarily on the pivotal global multicenter Study E2202 and supportive data from the single center pilot Study A2101J. No pooling of data was performed.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:

Compelling and consistent evidence for the clinical benefit of tisagenlecleucel in patients with r/r FL was indicated in pilot Study A2101J and this was subsequently confirmed in the pivotal Study E2202. Results from each trial are presented above.

The FDA's Assessment:

The efficacy data from Study E2202 was evaluated as a part of this supplemental BLA review. No pooling of efficacy data was performed from other studies including A2101J.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Compelling and consistent evidence for the clinical benefit of tisagenlecleucel in patients with r/r FL was observed in the pivotal Study E2202 compared with non-CAR-T standard of care for patients with r/r FL in a third- or later-line setting, where there is still a clear unmet medical need for deep and durable responses. Durable responses and prolonged PFS were also demonstrated in the pilot Study A2101J in the 5-year follow-up (5-year PFS: 43%).

Key benefits from Study E2202 are the following:

High response rates

CRR per IRC assessment, primary endpoint for this study, was 69.1% (95% CI: 58.8, 78.3) and 68.9% (95% CI: 58.3, 78.2) for the EAS and mEAS, respectively.

Robustness of CRR was further confirmed by a series of predefined sensitivity and subgroup analyses, with CRRs ranging from 59.0% to 68.9% across different high risk subgroups, i.e., patients with high FLIPI, bulky disease at baseline, patients belonging to POD24 group, patients who received >4 prior lines of treatment or prior bridging therapy, patients previously exposed to PI3K inhibitors, patients who relapsed <12 months after autologous HSCT and patients refractory to last line of prior therapy.

CRR has been shown to be a surrogate endpoint for PFS and OS in FL after first-line therapy. Patients who achieve a CR have been observed to have a longer PFS and OS compared to patients who did not achieve a CR. This suggests that specifically for CAR-T treatments, CRR is more likely to predict PFS and OS benefit than ORR (CR+PR) and represents a more relevant endpoint for physicians and patients.

Durable responses

The median DOR was not reached and the probability of event-free survival was 72.9% (95% CI: 61.3, 81.5) and 71.9% (95% CI: 59.0, 81.3) at Month 12 for the EAS and

mEAS, respectively, indicating sustained and deep disease control over time with a one-time infusion. DOR was longer in patients who achieved a CR, compared to those who achieved a PR. At Month 12, the Kaplan-Meier estimated probability of DOR (84.1% vs. 17.3%) for patients achieving CR were higher than for patients achieving PR as BOR.

Prolonged PFS

The 12-month PFS was 67.0% (95% CI: 56.0, 75.8) and 68.0% (95% CI: 56.8, 76.8) for the EAS and mEAS, respectively, and can be interpreted as estimated proportion of patients in CR or PR at Month 12. Tisagenlecleucel demonstrated an improvement in PFS compared with currently available non-CAR-T options which showed a median PFS of maximum of 14 months. At Month 12, the Kaplan-Meier estimated probability of PFS was longer among patients who achieved CR vs those who achieved a PR (85.5% vs. 25.7%).

Prolonged OS

The 12 months OS was 95.3% and 96.4% for the EAS and mEAS, respectively. Median OS was not reached.

One-time treatment

Tisagenlecleucel is administered as a single infusion. This is a key advantage compared to non-CAR-T treatments which consist either of several cycles of chemoimmunotherapy or of a chronic treatment needed until progression of disease or intolerance.

Stabilization of QoL

Quality of life of patients infused with tisagenlecleucel showed a general improvement over time. The rarity of long-term toxicities due to the one-time infusion, together with the durability of responses translate into less out-patient accesses and less hospitalizations for AEs or new anti-lymphoma therapies. These factors may play a key role in maintaining an improved QoL long term.

The FDA's Assessment:

Based on the totality of efficacy data reviewed in previous sections of this memo, the response rates with associated durability of tisagenlecleucel for treatment of adult patients with r/r FL after two or more lines of systemic therapy, represent clinically meaningful efficacy and evidence to support a meaningful therapeutic advantage in the context of available therapy for this indication. In addition, the data is comparable to current CAR-T cell therapy, axicabtagene ciloleucel, under accelerated approval.

8.2. Review of Safety

The safety evaluation for this submission is based on data from 97 subjects who received a tisagenlecleucel infusion in the pivotal Study E2202 as of the data cutoff date of 29-Mar-2021. Supportive data are derived from publications of pilot Study A2101J.

8.2.1. **Safety Review Approach**

Safety evaluations are available from the Study E2202 for all patients who received tisagenlecleucel (Safety set). In addition to the cumulative safety data from Study E2202, safety data were derived from 3 epochs post-tisagenlecleucel infusion: the initial 8-week period, the periods between 8 weeks and 1 year, and subsequently after 1 year. This analysis serves to delineate AEs that occurred within 8 weeks of infusion, in line with the previous evaluation performed in the pivotal trials in the indications adult r/r DLBCL and pediatric/young adult r/r ALL. AEs were categorized based on their time of onset.

Safety data include AEs, immunogenicity, laboratory abnormalities, ECGs, performance status, and height, weight, and vital signs. Safety evaluations are described in Study E2202 CSR-Section 9.5.3.

Subgroup analysis for age, race, gender, and ethnicity were performed (Study E2202 CSR-Section 9.7.2).

Data from Study A2101J are derived from publications in the public domain. Study A2101J provides safety data on 38 patients diagnosed with DLBCL (n = 24) or FL (n = 14), although safety data are not delineated by disease group. Of note, the majority of safety data are reported in the first publication in which 28 patients were treated, including 14 FL patients (Schuster et al 2017). A publication with 5-year follow-up reports limited additional safety data on an increased population of 38 patients (Chong et al 2021).

The FDA's Assessment:

The administration of CAR T cell is preceded by lymphodepleting chemotherapy. In addition, the subjects may receive other concomitant medications, which may potentially make it difficult to definitively establish the causality of adverse events occurring after the CAR T cell therapy. During this safety review, adverse drug reactions (ADRs) are defined as any treatment emergent adverse event (TEAE) with onset or worsening after the start of tisagenlecleucel infusion regardless of perceived relationship and causality with the investigational product. The Applicant reported AEs by preferred terms, which may underestimate the incidence of some AEs. To minimize such underestimation of AE, FDA grouped preferred terms that represent the same disease process (Please see Appendix 17.3 for the list of FDA Group Terms). The reviewer utilized a grouping strategy for comprehensive analyses of AEs that is consistent with the grouping practices for review of similar agents within this class of therapies.

In general, all grade AEs were counted by maximum toxicity (max tox) grade (i.e.,

multiple incidences of the same AE in one subject are counted once at the worst grade for this subject). For example, for Grade 3 AEs, the number of subjects who experienced any event with max tox Grade of 3 counted. This is different from the number of subjects who had a Grade 3 event, which is typically larger, as some will also have Grade 4 or 5 events.

The clinical safety review was primarily based on analysis of data submitted for the safety analysis set which comprised 97 subjects enrolled and treated with a single dose of tisagenlecleucel in the E2202 Study. The safety population consisted of all subjects with r/r FL (N=97) with a data cutoff date of 29 March, 2021. Analyses were performed using JMP 16 (SAS Institute, Inc.). Table 25 below summarizes the demographics and baseline characteristics of the safety population. Overall, among all subjects, the median age was 57 years (range: 29 to 73 years), 34% were female, 75% were White, 13% were Asian, and 1% were Black or African American. Furthermore, the review process also involved the review of 120-day safety report submitted by the applicant on 12 August 2021 with the data cutoff date of 03 August 2021.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

Study E2202

The median duration of follow-up post-infusion was 16.59 months (range: 10.3 to 25.7).

All 97 patients in the Safety set received a single dose of tisagenlecleucel. The median number of CAR-positive viable T cells administered was 2.06×10^8 cells (range: 0.1 to 6.0×10^8). The median total viable cell count was 12×10^8 cells (range: 0.4 to 34.0×10^8).

Study A2101J

In Study A2101J, the longest follow-up available is for a median of 60.7 months (5.1 years). All patients were infused with a dose 1 to 5 x 10^8 CAR-T-cells (Chong et al 2021).

The FDA's Assessment:

The FDA's safety review primarily included review of 97 subjects treated with tisagenlecleucel in study E2202. The primary data for study A2101J was not included as a part of BLA submission. Therefore, the review did not include A2101J study.

Relevant characteristics of the safety population:

Study E2202

Table 30: Applicant/FDA Reviewer: Demographics and baseline characteristics

Demographic variable	All leukhapheresed, N=98 n (%)	Safety analysis population N=97
Age at study entry (years)		
n	98	97
Mean (SD)	56.5 (10.34)	56.5 (10.39)
Median	57.5	57.0
Q1-Q3	49.0-64.0	49.0-64.0
Min-Max	29-73	29-73
Age at study entry category -n (%)		
18-<65 years	74 (75.5)	73 (75.3)
65-≤ 85 years	24 (24.7)	24 (24.7)
Sex -n (%)		
Male	65 (66.3)	64 (66.0)
Female	33 (33.7)	33 (34.0)
Race -n (%)		
White	74 (75.5)	73 (75.3)
Asian	13 (13.3)	13 (13.4)
Japanese	9 (9.2)	9 (9.3)
Indian	2 (2.0)	2 (2.1)
Missing	2 (2.0)	2 (2.1)
Black or African American	1 (1.0)	1 (1.0)
Missing	10 (10.2)	10 (10.3)
Ethnicity -n (%)		
Not Hispanic or Latino	84 (85.7))	84 (86.6)
Hispanic or Latino	3 (3.1)	2 (2.1)
Not Reported	11 (11.2)	11 (11.3)
ECOG performance status -n (%)		
0	56 (57.1)	55 (56.7)
1	39 (39.8)	39 (40.2)
2	3 (3.1)	3 (3.1)
Source: FDA Reviewer's analysis of BLA 125646/663 ADSL dataset, Study E2202 CSR-Table 14.1-4.1, Table 14.1-4.3		

The FDA's Assessment:

The demographic characteristics of the subjects included in safety analysis population (i.e., all treated subjects) is similar to the demographics of the intention to treat subjects

(i.e., all leukapheresed subjects). In summary, about 2/3 of the subjects were of <65 years of age; more were men than women, most were White race and non-Hispanic/Latino ethnicity. There were limited participation of subjects from African American, Hispanic and other ethnic backgrounds.

Study A2101J

Among the 14 patients with FL in Study A2101J, the median age was 59 years (range: 43-72 years). Half of the patients were female (7/14) (Schuster et al 2017).

The FDA's Assessment:

As noted above, the primary data from Study A2101J was not submitted with this application. Therefore, we did not perform primary analysis of A2101J data.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Study E2202

Table 31: Applicant/FDA Reviewer: Primary disease history and prior antineoplastic therapies

Disease history	All leukhapheresed subjects N=98 n (%)	Safety analysis population N=97 n (%)
Diagnosis of disease – n (%)		
Follicular lymphoma	98 (100)	97 (100)
Stage at time of study entry – n (%		
Stage III	26 (26.5)	21 (21.6)
Stage IV	58 (59.2)	56 (57.7)
Bone marrow involvement at study entry- n (%)		
Yes	37 (37.8)	37 (38.1)
No	60 (61.2)	59 (60.8)
Missing	1 (1)	1 (1.0)
Number of prior lines of antineoplastic therapy		
Median (min – max)	4.0 (2.0 – 13.0)	4.0 (2.0-13.0)
Progression of disease within 24 months (POD24) from first-line anti-CD20 mAb containing therapy – n (%)	61 (62.2)	61 (62.9)
Bulky disease at baseline – n (%)		
Yes	62 (63.3)	62 (63.9)
Primary refractory- n (%)	28 (28.6)	28 (28.9)
Treatment density		

Disease history	All leukhapheresed subjects N=98 n (%)	Safety analysis population N=97 n (%)
n	98	97
Mean (SD)	1.72 (1.165)	1.73 (1.171)
Median (min – max)	1.40 (0.14 – 5.65)	1.41 (0.14-5.65)
≥ 3FLIPI (High) score at study entry	59 (60.2)	58 (59.8)
Treatment density: derived as time from initial diagnosis to study entry (year)/ number of lines of prior therapy Source: Study E2202 CSR Table 14.1-5.1, Table 14.1-5.3		

The FDA's Assessment:

The disease characteristics in subjects included in safety analysis population appears similar to the intention to treat (i.e., all leukapheresed) population. The proportion of high-risk groups such as Stage IV disease, POD24 group and patients with high FLIPI scores were similar as well.

Concomitant medications or treatments

Concomitant medications administered during Study E2202 were representative of those routinely prescribed for patients with r/r FL, and/or for other illnesses commonly encountered in populations of a similar age. These patients typically have several ongoing comorbidities requiring ongoing treatment.

At the time of the current data cut-off, all patients in the Infused set with one exception received non-study concomitant medications. The most commonly used concomitant medications (in >30% of patients) by ATC class are listed below, presented in decreasing order of frequency (Study E2202 CSR-Section 10.5):

- Anti-infectives for systemic use in 93.8% of patients (primarily sulfamethoxazole/ trimethoprim [42.3%])
- Alimentary tract and metabolism medications in 79.4% of patients (primarily ondansetron [32.0%])
- Nervous system medications in 71.1% (primarily paracetamol [53.6%])
- Blood and blood-forming organs medications in 58.8% (primarily enoxaparin [22.7%])
- Dermatological in 50.5% (primarily acyclovir [27.8%])
- Musculoskeletal system medications in 50.5% (primarily allopurinol [40.2%])
- Antineoplastic and immuno-modulating agents in 47.4% (primarily filgrastim [25.8%], which was given following the restrictions defined by the [Study E2202 protocol Section 6.4])
- Cardiovascular system medications in 37.1% of patients

Seventeen patients (17.5%) in the Infused Set received at least one anti-cytokine medication for CRS. All 17 patients received tocilizumab and 4 of them also received corticosteroids (Study E2202 CSR-Section 10.5).

Bridging therapy

Of the 97 patients infused, 44 patients (45%) received optional antineoplastic bridging therapy prior to tisagenlecleucel infusion. The most commonly used agents (in ≥ 5% of patients) were rituximab (21.6%), dexamethasone (11.3%), gemcitabine (10.3%), oxaliplatin (7.2%), prednisolone (7.2%), etoposide (6.2%), cyclophosphamide (5.2%) and vincristine (5.2%). Furthermore, 2 patients received radiotherapy alone (Study E2202 CSR-Section 10.5.1).

Lymphodepleting chemotherapy

All infused patients received lymphodepleting chemotherapy prior to tisagenlecleucel infusion. Ninety-two of them received fludarabine + cyclophosphamide and 5 received bendamustine (Study E2202 CSR-Section 10.5.2).

Study A2101J

Disease characteristics

Among the 14 patients with FL, the median ECOG PS was 0. Twelve (86%) of patients had advanced disease and 9 patients (64%) patients had elevated LDH. The median number of previous treatments was 5; 3 patients had undergone prior autologous HSCT, and 1 patient had undergone prior allogeneic HSCT. Eight (57%) patients were considered double refractory (Schuster et al 2017).

Concomitant medications

Lymphodepleting chemotherapy included bendamustine; cyclophosphamide alone or in combination with fludarabine or radiation therapy; carboplatin+gemcitabine and modified EPOCH (doxorubicin, etoposide, cyclophosphamide) (Schuster et al 2017).

Adequacy of the safety database:

The FDA's Assessment:

The safety data from Study E2202 adequately represents the target population and allows for an informed assessment of the safety profile of tisagenlecleucel and evaluation of the benefit-risk in adult patients with r/r FL after two or more lines of therapy. The applicant also includes safety data for Study AJ2101, derived from the published literature.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The safety evaluation is based on data from the extended follow-up analysis (data cutoff date of 29-Mar-2021), when at least 90 patients were infused with tisagenlecleucel and had completed 12 months follow up from infusion, or discontinued earlier. The database was locked on 07-May-2021 after all the necessary actions had been completed and the database had been declared to be complete and accurate. The submission contains information previously discussed with the Agency, e.g., narratives, datasets.

Categorization of Adverse Event

Adverse events from Study E2202 were coded using MedDRA version 24.0; AE severity was graded using CTCAE version 4.03, except for CRS events that were graded by the Lee grading system (2014).

Full information about the definition of AEs, SAEs, AESIs and the procedures for reporting them are presented in Study E2202 CSR-Appendix 16.1.1-Protocol-Section 8. Detailed AE reporting requirements during the periods of screening, pre-treatment and treatment and follow-up are outlined in Study E2202 CSR-Appendix 16.1.1-Protocol-Appendix 3-Section 14.3.

Routine Clinical Tests

In Study E2202, safety was monitored by assessing the following parameters:

- Physical examination
- Vital signs
- Height, weight, and BMI
- ECOG performance status
- Immunogenicity against tisagenlecleucel
- Laboratory evaluations
  - Local clinical lab parameters: hematology, chemistry, urinalysis, coagulation, pregnancy screen, influenza, viral serology, serum immunoglobulin levels)
  - Central clinical lab parameters: CD19 testing, FL histology confirmation and grade determination, rituximab concentrations, tocilizumab PK, other non-rituximab anti-CD20 (e.g. ofatumumab), bone marrow aspirate/biopsy, B cell and T cell levels, RCL (vesicular stomatitis virus-glycoprotein), cytokines, immunogenicity, tisagenlecleucel cellular kinetics, tumor clonal typing, persistence of tisagenlecleucel transgene sequences in relevant tissues, peripheral blood molecular characterization, minimal residual disease, additional assessments.
- Cardiac assessments - ECG and cardiac imaging through MRA/MUGA/ECHO
- Pregnancy assessments
- AE data collection through Month 12 with modified AE reporting after the Month 12 visit (see Study E2202 CSR-Appendix 16.1.1-Protocol-Appendix 3-Section 14.3 for

details)

8.2.4. **Safety Results**

Deaths

Study E2202

During the course of E2202, a total of 7 fatalities were recorded in this trial at the time of the 29-Mar-2021 data cutoff date. No death occurred in the initial 30 days from tisagenlecleucel infusion. Five patients died due to progression of the underlying disease.

The remaining two fatalities occurred more than 1 year post tisagenlecleucel infusion (Study E2202 CSR-Section 12.2.1, Table 14.3.1-3.1); both patients had achieved a CR at Month 3 and were in ongoing response at time of death.

The FDA's Assessment:

There were no deaths within 30 days after tisagenlecleucel infusion. Total of seven deaths occurred till the data cutoff date, 29 March 2021.

Narratives of deaths not due to disease progression:

Subject (b) (6) : Death due to CRS on day 368;cause of death updated to HLH/MAS following additional information

- 72-year-old male patient, who received tisagenlecleucel at a dose of 1.1 × 108 CAR positive viable T-cells.
- Developed one episode of CRS on Day 7, which resolved on Day 30.
- Achieved CR at month 3 assessment and was in ongoing CR at the last assessment at month 12, 2 weeks before death.
- On Day 345 in the setting of ongoing pancytopenia and pneumonia, the patient had hypotension (60 mm Hg) that was attributed to sepsis or hypercytokinemia, with concurrent grade 3 encephalopathy.
- An initial brain MRI was negative for any abnormalities. Antibiotics, dexamethasone, and noradrenaline were initiated, and the patient was subsequently intubated due to respiratory failure.
- The patient's general condition continued to worsen despite the administered therapies.
- On Day 368, the patient had a severe episode of hypotension concurrent with pyrexia.
- No bacterial agents were isolated to indicate sepsis and work-up for autoimmune diseases was negative.

- A second brain MRI was performed showing a hygroma of unclear etiology as no trauma was reported.
- By means of exclusion, the Investigator diagnosed CRS.
- Reported ferritin levels were **5346 µg/L (high),** and **CRP was 0.28 mg/dL (high**). A cytokine panel was not performed.
- The treatment included vasopressin initially for progressive hypotension, tocilizumab (8 mg/kg, 2 doses) and high-dose corticosteroids (methylprednisolone 1 g). On Day 375, adalimumab (1 dose) and antithymocyte immunoglobulin (1 dose) were administered.
- The patient died on the same day due to multiorgan failure despite four lines of treatment for CRS.
- In the absence of a definitive diagnosis of sepsis or autoimmune disorder, the Investigator attributed the death to CRS. The Investigator suspected a causal relationship between tisagenlecleucel and the death.

Novartis' comment: Transgene levels at Month 3 were 96 copies/µg, and at Month 6 and Month 9 (6 and 3 months before the death, respectively) were below the limit of sensitivity, which makes a new onset of CRS at Month 12 due to tisagenlecleucel unlikely. Since a blood sample for transgene and cytokine analysis were not collected at Month 12 and in the absence of supporting investigations at the time of the event, the causality of fatal CRS was conservatively considered not assessable with tisagenlecleucel. In addition, pancytopenia and pneumonia further confounded the assessment. Autopsy results were not available at the time of the study report.

The FDA's Assessment:
We requested information on the autopsy result on the deceased subject. Per the applicant, the autopsy report was received from the site on 17-Nov-2021. The cause of death was concluded to be multiple organ failure.
Main parameters:
1. Follicular lymphoma (FL) (post chemotherapy, autologous peripheral blood stem cells transplant, radiotherapy, CAR-T therapy. No recurrence)
2. Macrophage activation syndrome (MAS) (Bone marrow, subcarinal lymph nodes, cervical lymph nodes, abdominal lymph nodes, spleen, liver, lung, tongue, esophagus, cerebrum, pons, medulla oblongata)
3. Cerebral demyelination inflammation (left frontal region)
4. Capillary leak syndrome

Other parameters:
1. Pneumonia bacterial
2. Diffuse alveolar damage (DAD)
3. Pulmonary oedema
4. Emphysema

There were no findings suggestive of atypical lymphocyte accumulation, follicular lymphoma relapse or vasculitis in these organs. In addition, when CD19 staining was

performed at the macrophage aggregation sites including the brain, no CD19 expressing cells were observed, and a causal relationship with CAR-T therapy could not be identified. The applicant concluded, '*some immunological abnormalities caused MAS after CAR-T therapy, which may have caused organ damage and massive effusion into a body cavity. It was considered that the subject eventually died with pneumonia and systemic condition aggravated.'*

Based on this autopsy result, we agree that the cause of death was not CRS but was multiorgan failure secondary to HLH/MAS. We asked the sponsor to make change in the proposed USPI to capture this event of Grade 5 HLH/MAS. Additionally, we recommended to include information about HLH/MAS in Section 5 Warnings and Precautions. The applicant has agreed with both recommendations.

Subject: (b) (6) **: (Death by euthanasia on day 302 due to progressive PML)**

- 57-year-old female patient received tisagenlecleucel at a dose of 1.8×108 CAR-positive viable T-cells.
- Achieved CR at Month 3 assessment.
- The patient experienced grade 1 CRS on Day 4 that resolved.
- On Day 11, the patient developed encephalopathy.
- On Day 12, the patient was diagnosed with encephalitis due to HHV6 and was treated with ganciclovir for 3 weeks and corticosteroids, after which the event resolved.
- Because the HHV6 DNA levels in CSF were at the limit of sensitivity, it was not fully diagnostic for HHV6 encephalitis, and the Principal Investigator considered that the neurological symptoms could have also been related to tisagenlecleucel and recorded 2 distinct events (encephalopathy grade 4 (immune effector cell-associated neurotoxicity syndrome) related to tisagenlecleucel, and HHV6 related encephalitis).
- Approximately 8 months after the infusion, the patient developed non-fluent aphasia and mild left paresis. The MRI showed multifocal white matter abnormalities and the CSF was negative for JC virus, although JC virus was isolated in the blood.
- Based on these findings, the Investigator provided a diagnosis of "possible" progressive multifocal leukoencephalopathy (PML) (radiological and clinical findings in keeping with PML, but viral screening on CSF negative, so a definitive diagnosis of PML was not possible).
- One month later, the patient presented with worsening of neurologic symptoms (grade 3), as well as new symptoms including ptosis and right hemiparesis.
- The patient chose euthanasia due to progressive neurological symptoms and died on Day 302.
- Last transgene levels performed on Day 250 ((b) (6)) were 139.6 copies/µg.
- The patient was in ongoing CR at Month 6.
- The last planned efficacy assessment (Month 9) was not performed due to deterioration of the neurological symptoms.

- The patient did not receive any further anticancer treatment post tisagenlecleucel infusion [Study E2202-Section12.2.1].

Novartis' comment: The causality between PML and tisagenlecleucel was considered not assessable. Prolonged immunosuppression due to multiple treatments for FL might have contributed to PML. Lack of autopsy results preclude a meaningful case assessment.

The FDA's Assessment:

Three additional deaths occurred during the 120-day safety update period with data cutoff date of 3 August 2021. One of these deaths occurred due to disease progression, and the other two deaths occurred due to AEs: one was due to metastatic squamous cell carcinoma and one due to pneumonia following new anti-lymphoma therapy (NALT) after progression of disease. Both deaths were not suspected by the investigator to be related to tisagenlecleucel. Please see below the narrative of these two deaths due AEs.

Subject (b) (6) : Death on day 897 due to metastatic squamous cell carcinoma

This was a 72-year-old White woman with Stage IV follicular lymphoma, histologic grade 1 or 2, diagnosed on (b) (6) . The patient had a FLIPI score at study entry of 4. The patient received two lines of prior therapy, including anti-CD20 monoclonal antibody and alkylating agents. The patient underwent prior autologous stem cell transplant on (b) (6) . The patient had the most recent relapse/progression on (b) (6) . The patient's past medical history included basal cell carcinoma (multiple locations: right lower leg, and mid back), squamous cell carcinoma (multiple locations: central back, left lower leg, right neck), and depression. Active medical condition included hypercholesterolemia and hypogammaglobulinemia. The patient underwent leukapheresis on (b) (6) . The patient was enrolled in the study on (b) (6) .

The patient received lymphodepleting chemotherapy consisting of fludarabine and cyclophosphamide from (b) (6) (Day −7) to (b) (6) (Day −5). The patient was infused with 1.4×10^8 tisagenlecleucel on (b) (6) (Day 1). On Day 6 ((b) (6)), the patient had headache (grade 2), which was resolved on the same day after the treatment with paracetamol.

On Day 115 ((b) (6)), the patient was diagnosed with recurrence of basal cell carcinoma (grade 2), and squamous cell carcinoma (grade 2) over right neck.

On Day 709 ((b) (6)), the patient developed basal cell carcinoma-second episode and squamous cell carcinoma-second episode (both grade 2). On the same day ((b) (6)), the patient underwent removal of nine skin lesions and recovered from the events (basal cell carcinoma-second episode, squamous cell carcinoma-second episode). On Day 868 ((b) (6)), the patient was diagnosed with poorly differentiated metastatic malignant squamous cell carcinoma (metastatic squamous cell

carcinoma, grade 5) and was hospitalized on Day 870 ((b) (6)). The patient did not receive antineoplastic treatment. On Day 897 ((b) (6)), the patient died due to the event (metastatic squamous cell carcinoma).

The Investigator considered no causal relationship between the events (headache, basal cell carcinoma-two episodes, squamous cell carcinoma-two episodes, pneumonia**,** metastatic squamous cell carcinoma) and the study treatment or lymphodepleting chemotherapy. The investigator considered causal relationship between metastatic squamous cell carcinoma and basal cell carcinoma with previous sun exposure.

Subject (b) (6) **: Death on day 721 due to pneumonia**:

This was a 56-year-old Indian male subject with Stage IV follicular lymphoma, histologic grade 1 to 2, diagnosed on (b) (6) . The patient had a FLIPI score of 3 at study entry. The patient received two lines of prior therapy, anti-CD20 monoclonal antibody and alkylating agents. No prior autologous stem cell transplant was performed. The patient had the most recent relapse/progression on (b) (6) . No past medical history was reported. Active medical conditions included hypertension, sinus tachycardia, back pain, and peripheral swelling.

The patient underwent leukapheresis on (b) (6) and was enrolled in the study on (b) (6) . While waiting for CTL019 manufacturing, the patient received bridging therapy with prednisolone, dexamethasone, rituximab, etoposide, carboplatin and ifosfamide.

The patient received lymphodepleting chemotherapy consisting of fludarabine and cyclophosphamide from (b) (6) (Day −14) to (b) (6) (Day −12). On (b) (6) (Day −12), the patient had pyrexia-first episode (grade 1), groin pain (left inguinal region, grade 2) and was hospitalized. On the same day ((b) (6)), the patient's blood cultures were negative, and the patient underwent ultrasound scan and aspirate sample collection from the left groin mass on (b) (6) (Day −9) with ANC at 5.6 × 103/µL. Treatment included piperacillin-tazobactam, paracetamol, oxycodone, and amoxicillin + clavulanic acid. On (b) (6) (Day −7), the event (groin pain) resolved.

The patient was infused with 2.5×10^8 tisagenlecleucel on (b) (6) (Day 1). On Day 85 ((b) (6)), the patient was diagnosed with progressive disease (new lesions in left neck posterior triangle, right occipital, right intra-parotid, focal soft tissue thickening-left posterolateral bladder). The patient continued to be followed for safety monitoring as per protocol.

On Day 106 ((b) (6)), the patient was hospitalized with pyrexia-second episode (grade 2, body temperature: 38°C), tachycardia with heart rate of 120 bpm. On the same day ((b) (6)), blood culture was normal, chest X-ray showed slightly patchy infiltrate left side and disease progression. Urine culture was normal and rapid Influenza test was negative. Treatment included amoxicillin-clavulanic acid, ceftriaxone, and azithromycin. On Day 109 ((b) (6)), the event (pyrexia-second episode) resolved, and the patient was discharged.

The patient received an experimental medication as post-treatment antineoplastic therapy (from (b) (6) to (b) (6) ; (b) (6) to (b) (6)), On Day 205 ((b) (6)), the patient was hospitalized for planned anti-neoplastic therapy administration. On Day 207 ((b) (6)), the patient was diagnosed with Grade 1 cytokine release syndrome-first episode.

The patient's planned hospitalization was prolonged. Treatment included paracetamol and piperacillin-tazobactam. On the same day ((b) (6)), blood culture was negative. On Day 209 ((b) (6)), the event (cytokine release syndrome-first episode) resolved, and the patient was discharged. On Day 212 ((b) (6)), the patient was hospitalized for planned anti-neoplastic therapy administration. On Day 214 ((b) (6)), the patient was diagnosed with Grade 1 cytokine release syndrome-second episode. On Day 214 ((b) (6)), blood culture was negative. Treatment continued with paracetamol. On Day 217 ((b) (6)), the event (cytokine release syndrome-second episode) resolved, and the patient was discharged.

On Day 219 ((b) (6)), the patient was hospitalized for planned anti-neoplastic therapy administration. On Day 221 ((b) (6)), the patient was diagnosed with cytokine release syndrome-third episode, which reached the highest grade of 1 and hospitalization was prolonged.

Treatment continued with paracetamol. The event (cytokine release syndrome-third episode) resolved on the day of onset **(** (b) (6) **)** and the patient was discharged on Day 222 ((b) (6)). The patient received antineoplastic radiotherapy to left neck and mediastinum from Day 405 ((b) (6)) to Day 416 ((b) (6)) followed by rituximab from Day 423 ((b) (6)) to Day 479 ((b) (6)) and lenalidomide from Day 405 ((b) (6)) to Day 493 ((b) (6) **) as** post treatment antineoplastic medications.

Last detectable transgene levels were recorded at month 6 (25.69µg/copies of DNA). Transgene levels were subsequently not detectable at month 9 and month 12. On Day 720 ((b) (6)), the patient was hospitalized due to pneumonia (maximum grade 5). The patient had 2-day history of fatigue, acute dyspnea, and septic shock. The patient was transferred to RMH ICU. The patient had progressive deterioration with respiratory failure, septic shock and had subsequent cardiac arrest. On the next day ((b) (6)), bicarbonate was 15 mmol/L, ANC count was 0 ×109/L (grade 4), sputum sample was positive for Pseudomonas aeruginosa and chest X-ray showed lower lobe consolidation. Treatment included caspofungin, human albumin, calcium chloride, sodium bicarbonate and filgrastim.

On Day 721 ((b) (6)), the patient died due to the event (pneumonia) associated with uncontrolled sepsis.

The Investigator considered no causal relationship between the events (pyrexia-two episodes, cytokine release syndrome-three episodes, pneumonia) and the study treatment or lymphodepleting chemotherapy. The event (pneumonia) was considered related to allogeneic haploidentical transplant and total body irradiation. [No further details on allogeneic transplant were available at time of this narrative update]

Study A2101J

As per the published information, one patient with a history of optic atrophy died due to encephalopathy that led to progressive neurologic deterioration in Study A2101J. This death was reported at the time of the 2-year follow-up (Schuster et al 2017). No additional deaths were reported in the 5-year follow-up (Chong et al 2021).

The FDA's Assessment:

Above information about Study A2101J is based on published information. No primary patient level data was submitted for review.

Serious Adverse Events

The Applicant's Position:

Forty-two patients (43.3%) experienced at least 1 SAE (Table 32) (Study E2202 CSR-Section 12.2.2).

Serious AEs were reported more frequently within the initial 8 weeks post-tisagenlecleucel infusion than in the periods from > 8 weeks to 1 year and > 1-year post-infusion (27.8% vs. 19.8% and 7.0%) (Study E2202 CSR-Section 12.2.2, Table 14.3.1-1.6).

Table 32: Applicant – SAEs post-tisagenlecleucel infusion, irrespective of study drug relationship, by preferred term and maximum grade reported in at least 2 patients (Safety set)

	All patients N=97	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of subjects with at least one event	**42 (43.3)**	**25 (25.8)**
Cytokine release syndrome	19 (19.6)	1 (1.0)
Pneumonia	8 (8.2)	5 (5.2)
Febrile neutropenia	6 (6.2)	5 (5.2)
Pyrexia	2 (2.1)	0
Encephalopathy	2 (2.1)	1 (1.0)
Infusion related reaction	2 (2.1)	2 (2.1)
Neutropenia	2 (2.1)	2 (2.1)
Pleural effusion	2 (2.1)	0
Squamous cell carcinoma	2 (2.1)	0
PTs are presented in descending frequency of all grades column. Source: Study E2202 CSR-Table 14.3.1-1.7		

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Study E2202

Of the 97 patients infused with tisagenlecleucel, 96 patients (99.0%) experienced at least 1 AE, irrespective of relationship to treatment.

The SOC with most commonly reported grade >3 AEs in ≥15% of the patients was blood and lymphatic system disorders (59.8%) investigations (29.9%) and infections and infestations (15.5%) (Study E2202 CSR-Table 14.3.1-1.2). Of note, AEs within the 'immune system disorders' SOC were also very commonly reported (55.7%) as this SOC includes CRS, which is an expected AE with tisagenlecleucel.

Irrespective of study drug relationship, the most frequently reported AEs (all grades) by PT in > 20% of the patients were CRS, neutropenia, anemia, headache, diarrhea, and white blood cell count decreased (Table 33).

The most common grade ≥ 3 AEs reported in ≥ 10% of patients any time post-infusion were neutropenia (42.3%), neutrophil decreased (17.5%), WBC decreased (17.5%), anemia (16.5%), febrile neutropenia (12.4%) and thrombocytopenia (11.3%).

Table 33: Applicant – AEs any time post-tisagenlecleucel infusion, irrespective of tisagenlecleucel relationship, by PT and maximum grade, and occurring in more than 10% of patients in all grades (Safety set)

	All patients N=97	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one AE	**96 (99.0)**	**76 (78.4)**
Cytokine release syndrome	48 (49.5)	1 (1.0)
Neutropenia	41 (42.3)	41 (42.3)
Anemia	25 (25.8)	16 (16.5)
Headache	24 (24.7)	1(1.0)
Diarrhea	21 (21.6)	1(1.0)
White blood cell count decreased	21 (21.6)	17 (17.5)
Pyrexia	19 (19.6)	1 (1.0)
Thrombocytopenia	19 (19.6)	11 (11.3)
Neutrophil count decreased	17 (17.5)	17 (17.5)
Fatigue	16 (16.5)	3 (3.1)
Nausea	15 (15.5)	2 (2.1)
Constipation	14 (14.4)	0
Hypogammaglobulinemia	14 (14.4)	1 (1.0)
Cough	12 (12.4)	0
Febrile neutropenia	12 (12.4)	12 (12.4)
Arthralgia	10 (10.3)	0
Platelet count decreased	10 (10.3)	6 (6.2)

A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
PTs are presented in descending frequency of the all grades column.
MedDRA version 24.0 and CTCAE version 4.03 have been used for the reporting of adverse events.
Source: Study E2202 CSR-Table 14.3.1-1.13

The majority of patients experienced AEs within the first 8 weeks of tisagenlecleucel infusion (92/97; 96.9%). In the period from Week 8 to 1 year post tisagenlecleucel infusion, 76/96 patients (83.3%) had an AE. Beyond 1-year post-tisagenlecleucel infusion, 19/97 (26.8%) patients had an AE (Study E2202 CSR-Table 14.3.1-1.2).

Similarly, the incidence of Grade ≥ 3 AEs was highest within the initial 8 weeks post-tisagenlecleucel infusion (reported in 69/97 patients; 71.1%); this incidence rate subsequently decreased to 42.7% (41/96 patients) between 8 weeks and 1 year post-tisagenlecleucel infusion, and further decreased to 9.9% (7/71 patients) > 1 year post-tisagenlecleucel infusion (Study E2202 CSR-Table 14.3.1-1.2).

The FDA's Assessment:

Adverse Drug Reactions: The following are proposed for inclusion in the tisagenlecleucel prescribing information Section 6.1. These adverse reactions are reported based on FDA Group Terms (GTs). Please note that laboratory abnormalities such as neutropenia, leukopenia, lymphopenia, thrombocytopenia and anemia are reported separately (Under 'Lab abnormalities' and are not included in this table).

Table 34: FDA Reviewer: Selected Adverse Reactions Any Time After Infusion Reported in ≥ 10% Following Treatment with tisagenlecleucel in Adult r/r FL (N = 97)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile Neutropenia	13	13
Gastrointestinal disorders		
Diarrhea	24	2
Nausea	16	2
Constipation	16	0
Abdominal pain[a]	10	1
General disorders and administration site conditions		
Fatigue[b]	27	3
Fever	19	1
Immune system disorders		
Cytokine release syndrome	53	0
Hypogammaglobulinemia[c]	18	1
Infections and infestations		
Infections-pathogen unspecified	38	12
Viral infectious disorders	18	5
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	25	1
Arthralgia	10	0
Nervous system disorders		
Headache[e]	25	2
Respiratory, thoracic and mediastinal disorders		
Cough[f]	19	0
Skin and subcutaneous tissue disorders		
Rash[g]	10	0

[a]Abdominal pain includes abdominal pain and abdominal pain upper.
[b]Fatigue includes asthenia, fatigue, and malaise.
[c]Hypogammaglobulinemia includes blood immunoglobulin G decreased and hypogammaglobulinemia.
[d]Musculoskeletal pain includes back pain, bone pain, flank pain, muscle discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and non-cardiac chest pain.
[e]Headache includes headache and migraine.
[f]Cough includes cough and productive cough.

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)

[g]Rash includes rash, rash maculo-papular, and rash papular.

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 18 were:

Blood and lymphatic system disorders: pancytopenia (3%), hemolysis[a] (2%), coagulopathy[b] (2%)

Cardiac disorders: tachycardia[c] (2%), arrhythmia[d] (4%)

Eye disorders: visual impairment[e] (4%)

Gastrointestinal disorders: vomiting (9%), stomatitis[f] (4%), abdominal distension (2%), dry mouth (2%)

General disorders and administration site conditions: edema[g] (9%), pain[h] (8%), chills (6%)

Immune system disorders: infusion related reaction (3%), graft versus host disease[i] (1%), hemophagocytic lymphohistiocytosis (1%)

Infections and infestations: bacterial infectious disorders (7%), fungal infectious disorders (2%)

Investigations: weight decreased (7%)

Metabolism and nutrition disorders: decreased appetite (8%), tumor lysis syndrome (2%)

Nervous system disorders: dizziness[j] (8%), motor dysfunction[k] (9%), peripheral neuropathy[l] (7%), immune effector cell-associated neurotoxicity syndrome (4%), encephalopathy (3%), tremor (3%)

Psychiatric disorders: sleep disorder[m] (6%), anxiety (2%), delirium (1%)

Renal and urinary disorder: acute kidney injury[n] (4%)

Respiratory, thoracic, and mediastinal disorders: dyspnea[o] (8%), pleural effusion (6%), oropharyngeal pain (5%), nasal congestion (2%), rhinorrhea (2%)

Skin and subcutaneous tissue disorders: pruritus (9%), night sweats (3%), erythema (2%), hyperhidrosis (1%)

Vascular disorders: hypotension[p] (9%), hemorrhage[q] (6%), hypertension (5%), thrombosis[r] (1%)

[a]Hemolysis includes hemolysis and hemolytic anemia.
[b]Coagulopathy includes coagulopathy and international normalized ratio increased.
[c]Tachycardia includes sinus tachycardia.
[d]Arrhythmia includes atrial fibrillation, atrioventricular block first degree, and electrocardiogram QT prolonged.
[e]Visual impairment includes blindness (preexisting progressive blindness, which initiated prior to start of lymphodepleting chemotherapy, further worsened after tisagenlecleucel infusion), vision blurred, and visual impairment.
[f]Stomatitis includes mouth ulceration and stomatitis.
[g]Edema includes edema peripheral, fluid retention, hypervolemia, localized edema, and peripheral swelling.
[h]Pain includes ear pain, pain, and pain in extremity.
[i]Graft versus host disease includes graft versus host disease in gastrointestinal tract and graft versus host disease in skin.
[j]Dizziness includes dizziness and syncope.
[k]Motor dysfunction includes dyskinesia, muscle spasms, muscular weakness, musculoskeletal stiffness, and myoclonus.
[l]Peripheral neuropathy includes dysesthesia, hypoesthesia, neuropathy peripheral, paresthesia, and peripheral sensory neuropathy.
[m]Sleep disorder includes insomnia.
[n]Acute kidney injury includes acute kidney injury and blood creatinine increased.
[o]Dyspnea includes acute respiratory failure, dyspnea, and dyspnea exertional.

[p]Hypotension includes hypotension and orthostatic hypotension.
[q]Hemorrhage includes blood blister, catheter site hemorrhage, contusion, epistaxis, hematochezia, hematoma, mucosal hemorrhage, oral blood blister, petechiae, and purpura.
[r]Thrombosis includes deep vein thrombosis.

The FDA's Assessment:

The overall AEs seen with tisagenlecleucel were consistent with those seen with other CD19 CAR T cell products, and are considered of acceptable severity given subjects' 'difficult to treat' and advanced disease with limited treatment available. No new safety signals, as well as, no excessive occurrence of known AEs were reported in study E2202.

Adverse Events of Special Interest (AESI)

The definitions of these AEs correspond to the important identified and important potential risks for tisagenlecleucel as per EU Risk Management Plan v4.0/US Pharmacovigilance Plan v5.0. The list of AESIs and their MedDRA search criteria are provided in Study E2202 CSR-Listing 14.3.2-2.2.

Important identified risks are:

- Cytokine release syndrome
- Serious neurological adverse reactions
- Infections
- Prolonged depletion of normal B cells/agammaglobulinemia
- Tumor lysis syndrome
- Hematological disorders including cytopenias

Important potential risks are:

- Cerebral edema
- Generation of replication competent lentivirus
- Secondary malignancies (including vector insertion site oligo/monoclonality)
- New occurrence or exacerbation of an auto-immune disorder
- Aggravation of graft-versus-host disease
- Transmission of infectious agents
- Decrease in cell viability due to inappropriate handling of the product

No AEs were reported for the following important potential risks:

- Cerebral edema
- Generation of replication competent lentivirus
- Transmission of infectious agents
- Decrease in cell viability due to inappropriate handling of the product

CRS

Fifty-one patients (53 %) had CRS. Of those, events in 50 patients occurred within the initial 8-week period post-tisagenlecleucel infusion (all within 30 days) and were either Grade 1 (n = 30; 31%) or Grade 2 (n = 20; 20.6%). All events resolved.

As per the original submission, two patients were considered to have had a late-onset CRS: one was fatal, and the other patient had Grade 1 CRS:

- Patient (b) (6) had 2 episodes of Grade 1 CRS, starting from Day 207 to Day 222 that occurred after documented disease progression (Day 85) and the start of a new antineoplastic investigational drug (T-cell engaging bi-specific antibody) on Day 120, considered to have induced the CRS. None of the CRS events were suspected to be related to tisagenlecleucel by the Investigator (Study E2202 CSR-Section 12.2.3).

- Patient (b) (6) had a first episode of CRS Grade 1 after tisagenlecleucel infusion which did not require anti cytokine treatment. Almost 1 year after infusion the patient developed encephalopathy, fever, persistent hypotension, and hypoxia in the setting of pancytopenia and pneumonia. The Investigator diagnosed CRS as diagnosis by exclusion, as work up for sepsis and autoimmune disorders was negative. The patient required multiple vasopressors, high flow oxygen and intubation and received tocilizumab, high dose steroids, and other 2 lines of treatment for CRS. Despite 4 lines of treatment for CRS this event led to death (Day 375 from infusion). The Investigator assessed the causality related to tisagenlecleucel.

  Novartis comment: Transgene levels at Month 3 were 96 copies/µg and were below the limit of sensitivity at Month 6 and Month 9 (6 and 3 months before the death, respectively), which makes a new onset of CRS at Month 12 due to tisagenlecleucel unlikely. Since a blood sample for transgene and cytokine analysis was not collected at Month 12 and supporting investigations at the time of the event were lacking, the causality of fatal CRS was conservatively considered not assessable with tisagenlecleucel. In addition, pancytopenia and pneumonia further confounded the assessment. Autopsy results were not available at the time of the study report.

Excluding the 2 late onset CRS, the median time from infusion to onset of CRS was 4.0 days (range: 1 to 14 days) and the median duration of CRS events was 4 days (range: 1 to 13 days). There was no influence of bulky disease at baseline on the incidence of CRS events (98.4% vs. 91.4%) (Study E2202-Table 14.3.1-2.1e). Systemic treatment, including anti-cytokine therapy with tocilizumab and/or corticosteroids, was required in 17 patients (33.0%); 2 patients (4%) required corticosteroids in addition to tocilizumab. [Study E2202-Section 12.2.3].

Update based on 120-day safety update and autopsy report on Subject (b) (6) : The cause of death on autopsy report was found to be multiorgan failure secondary to hemophagocytic lymphohistiocytosis/Macrophage activation syndrome (HLH/MAS). Accordingly, the earlier report of Grade 5 CRS event was replaced with Grade 5 HLH/MAS. Additionally, the description of HLH/MAS was added on Section 5 Warnings

and Precaution.

Table 35: Applicant – CRS post-tisagenlecleucel infusion (Safety set)

	All subjects N=97
Cytokine release syndrome (CRS) - n (%)	
No	50 (51.5)
Yes[1]	47 (48.5)
Maximum CRS Grade (Lee grading system) - n (%)	
Grade 1	26 (26.8)
Grade 2	20 (20.6)
Grade 3	0
Grade 4	0
Grade 5	1 (1.0)
Among subjects with CRS (first episode only)[2]	
Time to onset of CRS (days)	
n	47
Mean (Standard deviation)	4.8 (2.91)
Median (min – max)	4.0 (1 – 14)
Duration of CRS (days)	
n	47
Mean (Standard deviation)	5.3 (3.82)
Median (min – max)	4.0 (1 – 24)
Concurrent infections – n (%)	**7 (14.9)**
Fevers (>38 degrees Celsius or >100.4 degrees Fahrenheit) - n (%)	**43 (91.5)**
Time to fever onset (days)	
n	39
Mean (Standard deviation)	5.0 (2.93)
Median (min – max)	4.0 (1 – 14)
Duration of fever (days)	
n	39
Mean (Standard deviation)	2.7 (2.04)
Median (min – max)	2.0 (1 – 8)
Admitted to ICU - n (%)	**4 (8.5)**
Time to ICU admission (days)	
n	4
Mean (Standard deviation)	7.3 (3.10)
Median (min – max)	8.0 (3 – 10)
Duration of ICU stay (days)	
n	4
Mean (Standard deviation)	3.8 (1.50)
Median (min – max)	4.0 (2 – 5)

	All subjects N=97
Hypotension that required intravenous fluids and/or vasopressors - n (%)	**19 (40.4)**
Intravenous fluid administration - n (%)	19 (40.4)
Vasopressor administration - n (%)	3 (6.4)
One vasopressor	3 (6.4)
More than one vasopressor	0
Vasopressin administration - n (%)	0
High dose vasopressors - n (%)	0
Hypoxia observed - n (%)	**9 (19.1)**
Hypoxia requiring oxygen supplementation - n (%)	9 (19.1)
Low-flow - n (%)	9 (19.1)
High-flow - n (%)	0
Non-invasive mechanical ventilation - n (%)	0
Invasive mechanical ventilation - n (%)	0
Subject dialyzed - n (%)	**0**
Total Parenteral Nutrition (TPN) used - n (%)	**3 (6.4)**
Disseminated intravascular coagulation (DIC) observed - n (%)	**0**
Bleeding observed - n (%)	**0**
Blood product support given for bleeding - n (%)	0
Other CRS-related organ toxicities - n (%)	**3 (6.4)**
Cardiac - n (%)	1 (2.1)
Respiratory - n (%)	0
Hepatic - n (%)	0
Renal - n (%)	1 (2.1)
Neurologic - n (%)	0
Skin - n (%)	1 (2.1)
Other - n (%)	0
Systemic anticytokine therapy given - n (%)	**16 (34.0)**
Tocilizumab	16 (34.0)
1 dose	8 (17.0)
2 doses	5 (10.6)
3 doses	3 (6.4)
Siltuximab	0
Corticosteroids	3 (6.4)
Other	0

[1] Patient (b) (6) was not captured in this table, for whom CRS was reported on Day 207 post-infusion and the CRS was related to another investigational drug (T-cell engaging bi-specific antibody).

[2]All percentages presented below are based on the number of subjects with CRS. Only the first CRS episode is summarized for each subject.

Source: Study E2202 CSR-Table 14.3.1-4.1

The FDA's Assessment:

In addition to information presented in Table 35 by the applicant, following additional subjects were identified to have a CRS event.

Table 36: FDA Reviewer - FDA Adjudication of CRS events (Additional Subjects Identified to have CRS)

Subject ID	FDA Comments	Final Adjudication
(b) (6)	Subject developed grade 1 hypotension from day -3 to day 7, and also developed grade 1 fever on day 7.	Add Grade 1 CRS from day 7 to 7
(b) (6)	Subject developed grade 2 fever day 10, and ended the same day.	Add Grade 1 fever: start day 10 and ended day 10
(b) (6)	Subject had fever from day 1 to day 3	Add Grade 1 CRS from day 1-3
(b) (6)	Subject had grade 1 fever from day 8 to 8	Add Grade 1 CRS from day 8 to 8
(b) (6)	Subject developed fever on day 1, and ended on day 7. However, the subject was diagnosed with CRS on day 3, and resolved on day 7.	Please change CRS onset to day 1.

Treatment of CRS:

Of the 51 subjects with CRS, 15 (29%) received systemic anticytokine therapy with tocilizumab; 2 subjects (4%) received corticosteroids in addition to tocilizumab. Three patients required 3 dosages of tocilizumab, 4 subjects required 2 dosages and 8 subjects required single dose of tocilizumab.

Neurologic toxicity (specific to the product class)

The Applicant's Position:

Thirteen events of serious neurological adverse reactions (SNARs; including both non-serious and serious AEs) were reported in 11 patients (11.3%) post-tisagenlecleucel infusion. In 9 patients these SNARs were reported within the initial 8 weeks post-tisagenlecleucel infusion. There were no fatalities attributable to SNARs. Among the 3 patients who had Grade ≥ 3 SNARs, two patients died due to complications attributable to other causes. These included Patient (b) (6), who had Grade 3 encephalopathy ongoing at time of death for late onset of CRS, and Patient (b) (6), who developed Grade 4 encephalopathy shortly after tisagenlecleucel infusion with subsequent resolution within 3 weeks and died due to euthanasia for possible PML. The former is described above, and the latter is described below:

- [Patient E2202-(b) (6)] experienced Grade 1 CRS followed by encephalopathy Grade 4 considered by the Investigator to be related to tisagenlecleucel, and HHV6 related encephalitis. Both events recovered within 3 weeks from onset. Approximately 8 months after the infusion, the patient developed non-fluent aphasia and mild left paresis. The MRI showed multifocal white matter abnormalities; CSF was negative for JC virus, although JC virus was isolated in the blood. Based on these findings the Investigator provided a diagnosis of "possible" progressive multifocal leukoencephalopathy (PML). One month later, the patient presented with worsening of neurologic symptoms (Grade 3) as well as new symptoms including ptosis and right hemiparesis. The patient chose euthanasia due to progressive neurological symptoms and died on Day 302.

  Last transgene levels performed on Day◦250 ((b) (6)) were 139.6 copies/ug.

  Novartis comment: The causality between PML and tisagenlecleucel was considered not assessable. Prolonged immunosuppression due to multiple treatments for FL might have contributed to PML. Lack of autopsy results preclude a meaningful case assessment

Based on FDA's definition of neurologic toxicity, 36 patients (37.1%) experienced an event within 30 days post-tisagenlecleucel infusion (3 patients [3.1%] experienced Grade ≥3 event) and 14 patients experienced an event >30 days post-tisagenlecleucel infusion (3 patients [3.1%] experienced Grade ≥3 event). The median time to onset of first neurologic event from tisagenlecleucel infusion was 7 days (range: 1 to 345) and median time to resolution was 4 days.

The FDA's Assessment:

Forty two out of 97 subjects (43%) developed 74 events of neurologic toxicities (NT) following tisagenlecleucel infusion, with worst grade 3 events in 5 subjects (5%) and worst grade 4 event in 1 subject (1%). There was no grade 5 neurologic toxicity following tisagenlecleucel infusion. Sixty two out of those 74 NE events (84%) occurred within 8 weeks following treatment with tisagenlecleucel. Thirty eight out of 42 subjects with NE (90%) had at least one neurologic event that occurred within 8 weeks after

tisagenlecleucel infusion. The median time to onset was 8 days days (range: 1-345 days) and the median duration was 5 days (range:1-79 days).

Table 37: FDA Reviewer: Neurologic events reported in study E2202

FDA Grouped Term	All grade, N=97	Grade 3 or higher
All neurologic events	42 (43%)	6 (6%)
Headache[a]	24 (25%)	2 (2%)
Dizziness[b]	8 (8%)	1 (1%)
Motor dysfunction[c]	8 (8%)	0 (0%)
Peripheral neuropathy[d]	7 (7%)	0 (0%)
Insomnia	6 (6%)	0 (0%)
Immune effector cell-associated neurotoxicity syndrome	4 (4%)	1 (1%)
Encephalopathy	3 (3%)	1 (1%)
Tremor	3 (3%)	0 (0%)
Anxiety	2 (2%)	0 (0%)
Delirium	1 (1%)	1 (1%)
Depression	1 (1%)	0 (0%)
Dysgeusia	1 (1%)	0 (0%)

[a]Headache includes headache, migraine
[b]Dizziness includes dizziness, syncope
[c]Motor dysfunction includes muscle spasms, muscular weakness, musculoskeletal stiffness, myoclonus, dyskinesia
[d]Peripheral neuropathy includes peripheral neuropathy, neuropathy peripheral, peripheral sensory neuropathy, paresthesia, hypoaesthesia, dysaesthesia

Source: FDA Reviewer's review of ADAE dataset, and CSR

Serious Infections

The Applicant's Position:

Infections occurring at any time post-infusion were reported in 48 patients (49.5%), 13 of whom (13.4%) had infections suspected to be related to tisagenlecleucel (Study E2202 CSR-Section 12.2.3).

Most of the infections were either Grade 1 or 2. Grade ≥ 3 infections were reported in 15 patients (15.5%), 8 of whom (8.2%) had AEs suspected to be related to tisagenlecleucel. There were no patients with Grade 4 or fatal infections (Study E2202 CSR-Listing 16.2.7-1.1). Infections were considered SAEs in 17 patients. One patient died due to euthanasia chosen for progressive neurological symptoms due to possible PML on Day 302 (see short narrative above).

The majority of the patients had infections either within 8 weeks (n=18 [18.6%]; 17 patients had an infection within 30 days post-tisagenlecleucel infusion) or in the period from >8 weeks to 1-year post-tisagenlecleucel infusion (38.5%). Only 5 patients had infections more than 1 year after the infusion (Study E2202 CSR-Section 12.2.3).

Infections were managed with standard supportive measures and antibiotics.

The FDA's Assessment:

Infections occurred in 50 (52%) of the 97 treated patients with FL: 20 patients (21%) experienced ≥Grade 3 infections including fatal infection in 1 patient (1%). We recommended incorporating this information in the proposed USPI.

Hypogammaglobulinemia

Post-tisagenlecleucel infusion, 16 patients (17%) developed hypogammaglobulinemia. One patient had a Grade 3 AE and none of the patients had Grade 4 AEs. The AEs were ongoing in 9 patients at the time of the data cutoff date or death.

Prophylactic IV immunoglobulins were administered to 32 patients.

Tumor lysis syndrome

Tumor lysis syndrome was reported in 2 patients (2%); both were Grade 3 events. One event started on Day 10 and the other started on Day 125. Both events resolved after rasburicase and/or allopurinol treatment (Study E2202 CSR-Section 12.2.3, Listing 16.2.7-1.1 and review of ADAE, ADCM datasets).

Hematological disorders including cytopenias

The Applicant's Position:

Seventy-six patients (78.4%) had hematological disorders including cytopenias, mostly of Grade ≥ 3 (74.2%) severity. Hematological disorders were suspected to be related to tisagenlecleucel in 42 patients (43.3%). Events in 9 patients were considered serious (Study E2202 CSR-Section 12.2.3, Listing 16.2.7-1.1).

The hematological laboratory parameters which worsened to Grade 3/4 post-baseline most commonly (in >50% of patients) were decreased neutrophils (45/67 patients, 67.2%), decreased lymphocytes (10/16 patients, 62.5%), and decreased leukocytes (26/49 patients, 53.1%) (Study E2202 CSR-Table 14.3-6.2).

Most events occurred within 8 weeks post-tisagenlecleucel infusion (75.3%) (Study E2202-Section 12.2.3); all these occurred within 30 days post-tisagenlecleucel infusion. The AEs were generally managed with standard of care such as blood products, growth factors and/or antibiotics, as recommended in the protocol.

Although Grade ≥3 hematopoietic cytopenia occurred in a majority of the patients, there was a high probability of resolution of these events at Month 6 (Table 38).

Table 38: Applicant – Resolution of hematopoietic cytopenias post-tisagenlecleucel infusion (Safety set)

	All patients

	N=97				
	Week 4 event[1] n (%)	By Month 6[2]		By Month 12[2]	
Parameter		Patients at risk	% Resolved probability	Patients at risk	% Resolved probability
WBC	13 (13.4)	2	84.6	1	92.3
Hemoglobin	3 (3.1)	0	100.0	0	100.0
Platelets	16 (16.5)	3	81.3	0	NE
Neutrophils	15 (15.5)	1	93.3	0	100.0
Lymphocytes	22 (22.7)	6	70.0	4	80.0

Based on laboratory results regardless of blood transfusion.
NE=Not estimable.
Week 4: defined as day 35 (i.e., Day 28 +7 days time-window for Day 28 visit).
[1] Number of patients with last value on or prior to Week 4 indicating Grade 3 or 4 cytopenia
[2] Resolution of cytopenia is defined as achieving lab results of Grade 2 or below.
% resolved probability is among patients with cytopenia at Week 4, obtained from the KM survival estimates
Source: Study E2202 CSR-Table 14.3-7.1a

The FDA's Assessment:

The prolonged cytopenias were defined as cytopenia which persisted beyond day 28 (+7 days window as allowed by the study). Grade 3 or 4 prolonged thrombocytopenia occurred in 17 % and neutropenia in 16% subjects.

Secondary malignancies

The Applicant's Position:

Secondary malignancies were reported in 4 patients (4.1%). These were (Study E2202 CSR-Section 12.2.3):

1. Grade 2 squamous cell carcinoma of the skin and Grade 2 basal cell carcinoma (Day 115) in one patient: Both were removed by surgery. Neither event was suspected to be related to tisagenlecleucel.
2. Grade 2 squamous cell carcinoma (Day 283) and Grade 2 malignant melanoma (Day 324) in one patient: These events resolved (medical therapy and surgery) by the data cutoff date. Although the events were suspected to be related to both LD chemotherapy and tisagenlecleucel by the Investigator, Novartis concluded that the transgene and RCL test results in blood and tissue samples obtained for this patient precluded transgene- or RCL-mediated clonal transformation.
3. Grade 2 Bowen's disease (Day 82) in one patient: The event was not suspected to be related to tisagenlecleucel. Treatment included betamethasone. The event was ongoing at the time of the data cutoff.
4. Grade 1 basal cell carcinoma (Day 185) in one patient: removed by surgery. The event was not suspected to be related to tisagenlecleucel.

The FDA's Assessment:

Two additional secondary malignancies were reported in 120-day safety update: one case of bladder transitional cell carcinoma and one case of metastatic squamous cell carcinoma. Both of these cases were not thought related to either lymphodepleting chemotherapy or tisagenlecleucel by the investigator.

New occurrence or exacerbation of an auto-immune disorder

The Applicant's Position:

Due to the broad MedDRA search definition for this AESI, PTs (such as hypogammaglobulinemia, encephalopathy, or hemophagocytic lymphohistiocytosis) have been retrieved which do not reflect true autoimmune disorders in the setting of CAR-T cell therapy but rather present commonly observed ADRs of tisagenlecleucel important identified risks discussed in previous sections.

At study entry, 25 patients had hypogammaglobulinemia, and 2 patients had blood immunoglobulin G decreased (Study E2202 CSR-Section 12.2.3).

No AE that would constitute autoimmune disease associated with tisagenlecleucel could be identified.

AEs retrieved for this risk were reported in 20 patients (20.6%), most of whom had hypogammaglobulinemia (n = 14), and which were managed by immunoglobulin treatment. Most events were of Grade 1/2 severity and resolved at the time of the data cut-off. One patient had Grade 3 hypogammaglobulinemia.

Aggravation of graft-versus-host disease

The Applicant's Position:

Graft-versus-host disease of both the skin and intestines was observed in 1 patient following allogeneic HSCT on Day 246 post-disease progression. Both events resolved. The events were not suspected to be related to tisagenlecleucel, but to the allogeneic transplant (Study E2202 CSR-Section 12.2.3).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

No patients discontinued Study E2202 due to adverse events at the time of the data cutoff.

Dose Interruption/Reduction Due to Adverse Effects (if applicable)

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The subjects enrolled in Study E2202 were treated with single dose of tisagenlecleucel. Therefore, no dose interruption or reduction due to adverse events occurred.

Laboratory Findings

The Applicant's Position:

- The most commonly observed post-baseline hematological abnormalities worsening to Grade 3 or 4 were decreased lymphocytes, decreased neutrophils, and decreased leukocytes not considered serious events by the Investigators.
- Post-baseline clinical chemistry abnormalities were mostly Grade 1 or 2. The most common clinical chemistry abnormalities which worsened to Grade 3/4 post-baseline were decreased phosphate (10.9%), increased glucose (5.4%), and decreased potassium (5.2%) (Study E2202 CSR-Table 14.3-6.1).
- Based on Kaplan-Meier analysis of hematological laboratory parameters, by Month 6 the probability of resolution of all the cytopenias ranged from 70% to 100%.
- Minor elevations of liver enzymes were observed in a limited numbers of patients - ALT or AST > 3 × ULN was noted in 6 patients, ALT or AST > 5 × ULN in 2 patients, and total bilirubin > 3 × ULN in 1 patient.
- One patient each had ALT or AST >10× ULN and ALT or AST >20× ULN. There were no patients meeting the criteria AST/ALT >3x ULN and TBL >2x ULN or experiencing serious hepatic events (Study E2202 CSR-Table 14.3-8.1).
- Findings below or above normal ranges for urinary parameters were infrequent (Study E2202 CSR-Listing 16.2.8-2.1).

The following are proposed for inclusion in the tisagenlecleucel prescribing information Section 6.1:

Table 39: Applicant – Grade 3 or 4 laboratory abnormalities occurring in >10% of patients following tisagenlecleucel infusion

Laboratory Parameter	**Grade 3 or 4 (%)**
Hematology	
Lymphopenia	87
Leukopenia	74
Neutropenia	71
Thrombocytopenia	26
Anemia	25

Biochemistry	
Hypophosphatemia	10
[a]CTCAE = Common Terminology Criteria for Adverse Events version 4.03.	

The FDA's Assessment:

This clinical reviewer does not agree with the method the applicant initially used to calculate the treatment emergent laboratory abnormalities. Therefore, our results differed significantly with the applicant's results. FDA's lab shift analysis was performed on 97 subjects who were treated with tisagenlecleucel. The evaluable number for each lab, rather than the total number of safety population, were used as denominator during calculation of frequencies. Our analysis included all subjects with a baseline and at least one post treatment value. Subjects must have at least one grade worsening on study to be counted in the analysis and only worse grade lab abnormality is included in our analysis. Of note, the above method of analyzing lab shift may potentially underestimate the true incidence of lab abnormalities in subjects without a baseline value, especially for labs that are not routinely done at baseline e.g., uric acid, coagulation profile etc. Therefore, we also included subjects who had missing pretreatment baseline laboratory toxicity grade (BTOXGRN) but had abnormal post treatment toxicity grade (ATOXGRN) as treatment emergent laboratory abnormality. Please note that baseline lab grade refers to value prior to treatment with tisagenlecleucel.

Following are all treatment emergent lab abnormalities observed in adult subjects with r/r FL. Please note that baseline lab toxicity grade refers to lab value prior to tisagenlecleucel infusion. (Highlighted section will be included in the USPI)

Table 40: FDA Reviewer: Treatment emergent laboratory abnormalities following tisagenlecleucel treatment in adult subjects with r/r FL

PARAMCD_FDA	Evaluable, N	All Grade, N	All grade, %	Grade 3 or higher, N	Grade 3 or higher, %
NEUT decreased	92	71	77%	58	63%
WBC decreased	97	49	51%	39	40%
PLAT decreased	97	57	59%	20	21%
HGB decreased	97	51	53%	19	20%
LYM decreased	91	17	19%	17	19%
PHOS decreased	93	40	43%	11	12%
GLUC increased	93	53	57%	6	6%
K decreased	97	30	31%	6	6%
APTT increased	92	21	23%	6	7%
URATE increased	96	33	34%	4	4%

CALC decreased	96	43	45%	3	3%
ALT increased	97	40	41%	3	3%
ALB decreased	96	32	33%	2	2%
CREAT increased	97	31	32%	2	2%
K increased	97	26	27%	2	2%
LYM increased	97	11	11%	2	2%
CALC increased	96	6	6%	2	2%
AST increased	97	33	34%	1	1%
SODIUM decreased	97	27	28%	1	1%
SODIUM increased	97	20	21%	1	1%
BILI increased	97	17	18%	1	1%
ALP increased	97	33	34%	0	0%
MG decreased	97	24	25%	0	0%
FIBRINO decreased	94	17	18%	0	0%
GLUC decreased	93	14	15%	0	0%
MG increased	97	5	5%	0	0%
INR increased	56	1	2%	0	0%

Based on above results, following lab abnormalities were recommended to be included in the USPI.

Table 41: FDA Reviewer - Laboratory Abnormalities occurring in > 10% of Patients Following tisagenlecleucel Infusion in Adult r/r FL Patients Based on CTCAE[a] (N = 97)

Lab Abnormality	**Grade 3 or 4 (%)**
Hematology	
Neutropenia	63
Leukopenia	40
Thrombocytopenia	21
Anemia	20
Lymphopenia	19
Biochemistry	

Hypophosphatemia	12

[a]CTCAE = Common Terminology Criteria for Adverse Events version 4.03.

*Evaluable population (n=91 to 97) for each laboratory value included number of patients who had both baseline (before tisagenlecleucel infusion) and at least one post tisagenlecleucel infusion on-study laboratory value available.

The FDA's Assessment:

120 Day Safety Update:

The 120-day safety update was submitted on August 12, 2021 with the date cut-off date of 03-Aug-2021. At the time of the data cut-off for this safety update, the median post-infusion follow-up was 21 months (range: 14.4 to 29.9 months); 76 of the 97 infused patients (78.4%) were still in study follow-up. Twenty-two patients discontinued from the study follow-up, one prior to infusion. All but four patients received tisagenlecleucel within the target dose range [SCS].

At the time of the data cut-off for the safety update, 10 patients had died during the study, including three new deaths that occurred during the safety update period. One was due to the study indication. The other two additional deaths were due to metastatic squamous cell carcinoma and pneumonia. The fatal pneumonia occurred after four new anticancer treatments for progressive disease, the last one being allogeneic transplant. The AE profile for Study E2202 remained consistent during the safety update follow-up period compared to the safety dataset submitted with the original submission. No new events of CRS were reported during this period. No new neurologic toxicities were noted during this period. One subject continued to have tremor which had onset on day 4 of the study. The number of AEs of infections occurring any time post-infusion increased from 48 (49.5%) to 50 (51.5%) during the safety update period. However, the number of grade ≥ 3 infections remained same. One additional case of prolonged depletion of normal B-cells/hypogammaglobulinemia (Grade 2) was reported in one patient during the safety update period. No new cases of tumor lysis syndrome or GVHD were reported during this period. Two additional secondary malignancies were reported during the safety update (bladder transitional cell carcinoma and metastatic squamous cell carcinoma). Neither case was suspected to be related to tisagenlecleucel by the investigator. No AEs of 'cerebral edema', 'generation of replication competent lentivirus' or 'transmission of infectious agents' were reported.

In conclusion, one additional case of fatal pneumonia occurred during the safety update period, which was not thought to be related to tisagenlecleucel by the investigator. Overall, the safety experience in patients with r/r FL treated with tisagenlecleucel remained consistent with the safety data submitted in the original sBLA submission. No new safety signals emerged.

Study A2101J

The most comprehensive description of the AE profile in Study A2101J is available from the 2-year follow-up. At this follow-up, most AEs were of grade 1 or 2 in severity with only a few grade 3 or 4 AEs, and only one grade 5 AE (Schuster et al 2017).

Sixteen of 28 patients experienced a CRS. Five patients had CRS events that were grade ≥3 in severity. One patient was treated with tocilizumab, experienced a rapid reversal of symptoms and had a complete response to treatment. No patients received glucocorticoids. No patient died due to CRS (Schuster et al 2017).

Eleven patients had neurotoxic events such as encephalopathy, delirium, tremor, cognitive disturbance, confusion, involuntary movements, memory impairment suspected to be related to tisagenlecleucel therapy. All the events were less than grade 3, except 3 events of grade ≥ 3 encephalopathy occurring in 3 individual patients. One 43-year-old male patient with prior history of optic atrophy developed CRS grade 2 and encephalopathy on Day 8 post tisagenlecleucel. He experienced protracted worsening of neurological disease and died from encephalopathy on Day 232. Post-mortem of this patient revealed diffuse gliosis with severe, widespread neuronal loss and degeneration of white matter but did not reveal a viral cause for the PML. The investigator stated that antecedent history of optic atrophy suggests that the patient might have had autoimmune CNS disease prior to receiving tisagenlecleucel. With the exception of this fatal event, the neurologic symptoms were self-limiting and resolved fully within 1 week (Schuster et al 2017, Chong et al 2021).

At the 5-year follow-up, limited safety data is available from 38 patients infused with tisagenlecleucel. Of note, 6 of 38 (16%) patients had secondary malignancies. No cases of RCL were detected (Chong et al 2021).

The FDA's Assessment:

As noted in previous sections, no primary data for study A2101J were submitted. Therefore, no formal safety analyses were performed on this study.

Vital Signs

The Applicant's Position:

Abnormal vital signs values, high fever in particular, were mainly associated with events of CRS. Abnormal values eventually returned to normal levels with supportive care and were reported as AEs when considered clinically relevant by the Investigator (Study E2202 CSR-Section 12.4.1).

Immunogenicity

The Applicant's Position:

Similar to traditional biologics, immunogenicity is evaluated for characterizing the safety of therapies for which potential immunogenicity may pose a safety risk. For this reason,

the impact of immunogenicity on cellular kinetics and safety was explored (Summary of Clinical Pharmacology-Section 2.8).

At baseline, 66.0% (64/97 patients) of the patients tested positive and 22.7% (22/97 patients) of the patients tested negative for anti-mCAR19 antibody. For some patients, the baseline anti-mCAR19 antibody status was not available. A patient was only defined as positive for tisagenlecleucel treatment-induced or -boosted anti-mCAR19 antibodies when the anti-mCAR19 antibody MFI at any time post-infusion was at least 2.28-fold higher than pre-infusion levels for patients whose baseline status was positive (boosted) or if the baseline status was negative but any post-baseline interpretation was positive (induced). Treatment-induced or boosted anti-mCAR19 antibodies were observed in 27 patients in the Cellular kinetics analysis set, while 56 patients did not show induced or boosted response (Study E2202 CSR-Section 11.2.6).

The geometric mean AUC0-28d was similar in both the groups, whereas, the geometric mean AUC0-84d and Cmax were observed to be 46% and 49.6% higher in patients with treatment-induced or boosted anti-mCAR19 antibodies post-tisagenlecleucel infusion (Study E2202 CSR-Section 11.2.6).

The pre-existing antibodies, i.e., at enrollment, or maximum fold change from baseline to post-infusion were not associated with any impact on clinical response. There was no apparent relationship between CRS grade and maximum fold change from baseline for anti-mCAR19 antibody levels. There were no grade 3/4 CRS events within 8 weeks of infusion (Study E2202 CSR-Section 11.2.6).

Treatment-boosted or treatment-induced anti-mCAR19 antibodies did not appear to have an impact on the in vivo expansion of CAR-positive T-cells and persistence or clinical response (Study E2202 CSR-Section 11.2.6).

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Cytokine release syndrome

The Applicant's Position:

CRS is one of the adverse reactions subject to the Risk Evaluation and Mitigation Strategy (REMS). This is discussed above under AESI.

8.2.5.2 Neurological toxicities

The Applicant's Position:

Neurological toxicities are one of the adverse reactions subject to the REMS. This is discussed above under AESI.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

No major differences in the incidence of AEs were observed across subgroups (age, gender, race, ethnicity, and bulkiness of the disease) (Study E2202 CSR-Section 12.1.3.5).

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:

Not applicable.

Human Reproduction and Pregnancy
The Applicant's Position:

Not applicable.

Pediatrics and Assessment of Effects on Growth (If applicable)
The Applicant's Position:

Not applicable.

The FDA's Assessment:
The study E2202 did not enroll any pediatric subjects. Therefore, this section is not applicable.

8.2.10. **Safety in the Postmarket Setting**

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

As of 29-Mar-2021 (data cutoff), tisagenlecleucel is approved in 41 countries/regions worldwide.

There were no new or changing safety signals based on the evaluation of safety data obtained during the Periodic Safety Update Report 5 reporting interval or cumulatively. A critical analysis of the efficacy and safety data revealed that the overall benefit-risk profile of tisagenlecleucel remains favorable.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Based on the safety experience with tisagenlecleucel, no update to the important risks is considered required for the proposed indication of r/r FL. Novartis will continue to apply the full spectrum of routine and additional pharmacovigilance practices and risk minimization activities, respectively, per the regional risk mitigation plans.

The FDA's Assessment:

REMS with ETASU will be implemented to ensure safe use in the postmarketing setting. Additionally, tisagenlecleucel has the potential for the serious risk of secondary malignancy due to replication-competent retrovirus used in its manufacturing and the potential for insertional mutagenesis. Furthermore, the patients with r/r FL represent a distinct patient population, compared to patients with r/r ALL or large B-cell lymphoma. Therefore, a separate long-term follow-up (LTFU) for safety with active surveillance in the r/r FL patient population after treatment with tisagenlecleucel will be required.

8.2.11. **Integrated Assessment of Safety**

The Applicant's Position:

No new safety signals emerged from the 113 patients with r/r FL infused in Studies E2202 and A2101J. The safety profile of tisagenlecleucel is well characterized and toxicity is manageable.

The profile of identified risks in Study E2202 was similar to that observed in the other NHL indication where tisagenlecleucel is approved. The key ones are:

Cytokine release syndrome

Most CRS events were of Grade 1 or 2 (50 patients; 53%). There were no Grade 3/4

CRS events. Except for 2 patients, CRS occurred within 8 weeks post-infusion, and resolved within 13 days from onset (median duration 4 days, range 1-13 days). CRS could be adequately managed with a CRS management algorithm in place as per Study E2202 protocol. Less than 10% patients required admission to ICU. Two patients had a late onset CRS, in one case CRS was due to a new antineoplastic treatment. In the other case, CRS had a fatal outcome, but the diagnosis was made by the Investigator by exclusion, while transgene levels were not quantifiable in preceding months; Novartis could not causally attribute the event to tisagenlecleucel.

Serious neurological adverse reactions

A total of 11.3% of patients experienced SNARs within 8 weeks of the infusion, including 3% with a Grade ≥ 3 event; all of these events resolved and there were no fatalities. One patient had SNARs beyond the initial 8-week period post-infusion: one case of delirium that was not related to tisagenlecleucel.

Infections

Infections occurring any time post-infusion were reported in 48 patients (49.5%), 13 (13.4%) of whom had infections suspected to be related to tisagenlecleucel (Study E2202 CSR-Section 12.2.3).

There were no patients with Grade 4 or fatal infections.

A patient developed possible grade 3 PML, in the aftermath of which, the patient chose euthanasia. It was not possible to definitively attribute this PML case to tisagenlecleucel, due to a lack of transgene level and autopsy results, no serological confirmation of the JC virus, and prolonged immunosuppression with multiple FL treatments.

Infections were managed with standard supportive measures and antibiotics.

Prolonged depletion of normal B-cells/agammaglobulinemia

Post-tisagenlecleucel infusion, 16 patients (16.5%) had prolonged depletion of normal B-cells/agammaglobulinemia.

These AEs were managed with prophylactic iv immunoglobulins. None of the AEs were serious or led to fatal infections (Study E2202 CSR-Section 12.2.3).

Hematological disorders including cytopenias

Seventy-six patients (78.4%) experienced hematological disorders, including cytopenias, post-tisagenlecleucel infusion. Kaplan-Meier analysis showed a high probability of resolution of any Grade ≥ 3 laboratory finding in the majority of patients by Month 6, indicating the transient nature of these events.

The safety profile of tisagenlecleucel is well-established in patients with DLBCL and ALL. No new safety signals were observed in the r/r FL population. The safety profile highlighted in the available published data for Study A2101J was in line with the known tisagenlecleucel safety profile.

The FDA's Assessment:

In general, the safety profile seen in Study E2202 appeared similar to what were previously reported in studies involving r/r ALL (Study B2202) and large B-cell lymphoma (C2201). Upon further review, events of hemophagocytic lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS) were reported in all three studies, although at a low rate. Most of these events occurred early after treatment with tisagenlecleucel. One event of HLH/MAS reported in study E2202 occurred late, and had a fatal outcome. We recommended including the information about this event in the label. Further, we also recommended to include the description of HLH/MAS in Section 5 Warnings and Precautions. The applicant has agreed with our recommendations.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

E2202 is a Phase II single-arm multicenter trial which evaluated the efficacy and safety of tisagenlecleucel in adult patients with r/r FL after two or more lines of systemic therapies. CRR was used as the primary efficacy endpoint. The study tested the null hypothesis of CRR being ≤ 15% at one sided cumulative 2.5% level of significance. Assuming the underlying CRR of 30% for tisagenlecleucel, a sample size of 90 was needed to provide at least 90% cumulative power to demonstrate statistical significance at one sided cumulative 0.025 level of significance.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Efficacy: The high ORR and CR rates with a median DOR of NE after all subjects (with the exception of one subject) in the primary efficacy population of 90 subjects with relapsed or refractory FL had had the opportunity to be followed up for a minimum of nine months after first objective response provides evidence of a reasonable likelihood of clinical benefit adequate to support accelerated approval of tisagenlecleucel for the proposed indication of adult patients with r/r FL after two or more lines of systemic therapy.

Safety: The CRS and neurologic toxicities were seen as expected, which were serious, life threatening, and potentially could be fatal. No death occurred due to CRS or neurologic toxicity. The treatment algorithms instituted to mitigate these AEs were effective and permitted the benefits of treatment to outweigh these risks. No new safety signals were identified in this study. Additionally, there is a theoretic risk of insertional mutagenesis and resultant secondary malignancies, and hence a long-term 15 years follow-up (LTFU) study to monitor for long term safety including secondary

malignancies, will be required.

1. To enhance safety, the following measures should be followed:
    a. The label should include a boxed warning for CRS and neurologic toxicity (NT), and the Warnings and Precautions sections outlines the grading and management algorithms for CRS and NT.
    b. REMS with ETASU to assure the safe use of tisagenlecleucel.
    c. A PMR study that a requirement to follow the subjects treated with tisagenlecleucel for short term and long term up to 15 years.

In summary, the study E2202 represents an adequate and well controlled trial that provides substantial evidence of effectiveness in the context of an acceptable safety profile in support of an accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

X	X
Primary Clinical Reviewer	Clinical Team Lead

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Advisory committee meeting was not conducted for this submission. No external consultations were required.

10 Pediatrics

The Applicant's Position:

The efficacy and safety of tisagenlecleucel in pediatric patients have not been studied. Tisagenlecleucel has orphan-drug designation for the treatment of FL, based on Request #DRU-2020-7651, granted on 16-Sep-2020. Due to the orphan-drug designation of tisagenlecleucel for this indication, it is exempt from Pediatric Research Equity Act requirements.

The FDA's Assessment:

The study E2202 did not enroll or treat any pediatric subjects. This is a supplemental BLA application seeking registration of tisagenlecleucel for the proposed indication of adults with r/r FL after two or more lines of systemic therapy. Tisagenlecleucel has orphan drug designation for treatment of r/r FL. Therefore, the application is exempt from Pediatric Research Equity Act (PREA).

11 Labeling Recommendations

The Applicant's Position:

The table below summarizes proposed revisions to the prescribing information. Please see labeling file in Module 1.14.1.3 for full changes.

Table 42: Applicant/FDA Reviewer - Proposed revisions to the prescribing information

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1 Indications and Usage		
1.3 Adult Relapsed or Refractory (r/r) Follicular Lymphoma (FL)	Proposed indication statement: Adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of therapy	Adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy
2 Dosage and Administration		
2.3 Administration	Addition of information pertaining to LD chemo	Please see Section 2.3 of the label
2.4 Management of Severe Adverse Reactions	Updated CRS management recommendation	Updated Table for grading and management of CRS and NT Included incidence, severity and duration of CRS and NT based on FDA's adjudication.
5 Warnings and Precautions	NA	Added Section 5.4 on HLH/MAS as an identified risk associated with tisagenlecleucel
5.1 Cytokine Release Syndrome	Added information from Study E2202	Please see Section 5.1 of the label
5.2 Neurological Toxicities	Added information from Study E2202	Please see Section 5.2 of the label
5.5 Serious Infections	Added information from Study E2202	Please see Section 5.6 of the label
5.6 Prolonged Cytopenias	Added information from Study E2202	Please see Section 5.7 of the label
5.7	Added information from	Please see Section 5.8 of

Hypogammaglobulinemia	Study E2202	the label
6 Adverse Reactions		
6.1 Adverse Reactions	Added information from Study E2202	Included ADRs and laboratory abnormalities based on FDA's adjudication using FDA Grouped Terms.
12 Clinical Pharmacology		
12. Pharmacokinetics/ Cellular Kinetics	Added information from Study E2202	No major revisions
14 Clinical Studies		
14.3 Adult Relapsed or Refractory (r/r) Follicular Lymphoma	Added information from Study E2202	Include efficacy data from E2202 study based on FDA's adjudication using primary efficacy population. Also include efficacy results of intention to treat (leukapheresed(population.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Tisagenlecleucel was originally approved with a Risk Evaluation and Mitigation Strategy (REMS) due to risk of serious and potentially life-threatening complications of CRS and neurologic toxicities (NT). REMS includes elements to assure safe use (ETSU), and requires that hospitals and associated clinics dispensing tisagenlecleucel be certified and have on-site, immediate access to tocilizumab, and health care providers involved in the prescribing, dispensing, or administering be trained to recognize and manage CRS and NT.
Refer to OBE review memo/Appendix C for the list of REMS modifications and recommendations.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Efficacy:
The clinical team recommends accelerated approval of tisagenlecleucel for the treatment of adult patients with r/r FL after two or more lines of systemic therapy. Additional data are needed to confirm the clinical benefit for consideration of conversion to regular approval. Therefore, we recommend the PMR as outlined below:

- A randomized phase 3 trial in patients with relapsed or refractory follicular lymphoma. Patients should be randomized to tisagenlecleucel or an investigator's choice of regimens consistent with the standard of care. The primary endpoint should be progression-free survival with secondary endpoints that include overall survival and objective response rate.

  - Final Protocol Submission: 12/2022
  - Study/Trial Completion: 03/2028
  - Final Report Submission: 09/2028

The applicant has proposed a global multicenter phase 3 trial with 1:1 randomization comparing tisagenlecleucel versus investigator's choice of standard of care. The study population will include adult patients with r/r FL grade 1-3A after two or more lines of treatment. Primary endpoint will be progression-free survival. The secondary endpoints will be complete response rate, overall response rate, duration of response, overall survival, and safety. Further discussion will be conducted as the applicant submits the clinical study protocol. Overall, the applicant's proposed study design elements are reasonable.

Safety:
The pharmacovigilance plan (PVP) requires a long term, prospective, non-interventional post marketing requirement (PMR) registry in subjects treated with tisagenlecleucel.

Both the 2017 initial approval of tisagenlecleucel BLA 125646/0 for ALL indication, and subsequent approval in 2018 of sBLA 125646/76 for DLBCL indication, included postmarketing requirements (PMRs) under Section 505(o) of the Federal Food, Drug, and Cosmetic
Act (FDCA) to conduct LTFU studies to evaluate the serious risk of secondary malignancies associated with the use of tisagenlecleucel in specific patient populations. The applicant is currently conducting postmarketing, prospective, multi-center, observational studies with 15-year LTFU, in:

- at least 1000 pediatric and young adult patients with relapsed / refractory B-cell acute lymphoblastic leukemia, and
- at least 1500 patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising

from follicular lymphoma.

Similarly, the applicant will be required to conduct a LTFU registry study in FL patient population. The applicant has submitted a preliminary plan to conduct such study. (Please see OBE review memo for details of the proposed LTFU study). In summary, the applicant has agreed to conducting a PMR in 300 adult patients with follicular lymphoma with a 15-year follow-up. The PMR was presented to the CBER Safety Working Group on January 13, 2022 by OBE review team and the applicant was notified that the registry study will be a PMR, which was acknowledged by the applicant (STN125646/663.38).

Under the study, healthcare providers and registry holders will report secondary malignancies to the applicant within 72 hours of diagnosis if the patient develops a secondary malignancy. The applicant will recommend collection of blood samples for CAR transgene and RCL. The applicant will also attempt to collect a portion of the sample from the secondary malignancy, if collected as part of standard care, for CAR gene and RCL.

The applicant has proposed the following milestones:
Final protocol submission: September 30, 2022
Study completion date: September 30, 2042
Final report submission: September 30, 2043

14 Deputy Director, DCEPT

X

15 Oncology Center of Excellence (OCE) Signatory

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

X _____

16 Division Director (DCEPT)

The Office of Tissues and Advanced Therapies (OTAT) concurs with OCE/clinical recommendation.

The applicant has provided substantial evidence of effectiveness and safety from an adequate, well controlled clinical study, as well as mechanistic evidence to support an indication for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

For Tejashri Purohit-Sheth, MD, Director, DCEPT:

X

17 Appendices

17.1. References

The Applicant's References:

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The FDA's Assessment:

Agree with above references. Please refer to the footnotes throughout the document for FDA's references and citations.

17.2. Financial Disclosure

The Applicant's Position:

Based on the financial disclosure information collected/reviewed, one investigator had financial information to disclose. This is summarized in the file located in Module 1.3.4.

The FDA's Assessment:

The financial disclosure forms FDA 3455 and 3454 with authorized signatures were

submitted under Module 1.3.4. as required per 21 CFR 54.4(a)(1) and (3).
No investigators were full or part time employees of Novartis. There were total of 430 investigators; 142 in the US and 288 outside the US. All US investigators (100%), and 285 outside US investigators provided financial disclosure forms. Disclosable financial interest was reported by one investigator. The applicant states that any bias resulting from these arrangement was minimized by independent data monitoring committee.

Covered Clinical Study (Name and/or Number): * CCTL019E2202 ("Study E2202")

The Applicant's position:

Please note the information entered below is based on financial disclosure information previously submitted to BLA 125646 with the original sBLA (27-Aug-2021; Sequence No. 0299) as well as updated information submitted with the 120-day Safety Update (15-Dec-2021; Sequence No. 0367).

Was a list of clinical investigators provided? **Novartis' comment**: Please refer to Section 6 of the financial disclosure information submitted to BLA 125646 with the original sBLA and the 120-day Safety Update (submission details are provided above)	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 438		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 **Novartis' comment**: Please refer to Section 5 of the financial disclosure information submitted to BLA 125646 with the original sBLA and the 120-day Safety Update		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with	Yes ☒	No ☐ (Request details from

details of the disclosable financial interests/arrangements? **Novartis' comment**: Please refer to Sections 5 and 8 of the financial disclosure information submitted to BLA 125646 with the original sBLA		Applicant)
Is a description of the steps taken to minimize potential bias provided? **Novartis' comment**: Please refer to Section 5 of the financial disclosure information submitted to BLA 125646 with the original sBLA	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason? **Novartis' comment**: This information was reported and summarized in Section 5 of the financial disclosure information submitted with the original sBLA and the 120-day Safety Update.	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above was filled by the applicant, and confirmed/edited by the FDA.

17.3. List of FDA Group Terms and Preferred Terms Used in This Review

Table 43: FDA Reviewer – Grouped Terms and Preferred Terms using while reporting adverse drug reactions

Grouped Term	Preferred Terms
Abdominal pain	Abdominal pain, abdominal pain upper
Acute kidney injury	Acute kidney injury, blood creatinine increased
Arrhythmia	Atrial fibrillation, atrioventricular block first degree, and electrocardiogram QT prolonged
Bacterial infectious disorder	Includes high level group term (HLGT) of Bacterial infectious disorders.
Cardiac failure	Cardiac failure, cardiac failure congestive, left ventricular dysfunction, right ventricular dysfunction.
Catheter site irritation	Catheter site irritation, catheter site related reaction
Coagulopathy	Coagulopathy, International normalized ratio increased
Cough	Cough, productive cough
Diarrhea	Diarrhea, colitis
Dizziness	Dizziness, syncope

Dyspnea	Acute respiratory failure, dyspnea, and dyspnea exertional
Edema	Edema peripheral, fluid retention, hypervolemia, localized edema, and peripheral swelling
Fatigue	Fatigue, malaise, asthenia
Fungal infectious disorders	Includes HLGT of Bacterial infectious disorders.
Graft versus host disease	Graft versus host disease in gastrointestinal tract, graft versus host disease in skin
Headache	Headache, migraine
Hemolysis	Hemolysis, hemolytic anemia
Hemorrhage	Blood blister, catheter site hemorrhage, contusion, epistaxis, hematochezia, hematoma, mucosal hemorrhage, oral blood blister, petechiae, and purpura
Hyperbilirubinemia	Blood bilirubin increased, hyperbilirubinemia
Hyperlipidemia	Dyslipidemia, Hypertriglyceridemia
Hypertransaminasemia	Alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased
Hypoalbuminemia	Blood albumin decreased, hypoalbuminemia
Hypotension	Hypotension, orthostatic hypotension
Hypogammaglobulinemia	Hypogammaglobulinemia, Blood immunoglobulin G decreased
Infections-pathogen unspecified	Includes HLGT of infections-pathogen unspecified
Leukopenia	Leukopenia, white blood cell count decreased
Lymphopenia	Lymphopenia, lymphocyte count decreased
Motor dysfunction	Muscle spasms, muscular weakness, musculoskeletal stiffness, myoclonus, dyskinesia
Musculoskeletal pain*	back pain, bone pain, flank pain, muscle discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and non-cardiac chest pain
Neutropenia	Neutropenia, neutrophil count decreased
Pain	Pain, pain in the extremity, ear pain,
Peripheral neuropathy	Neuropathy peripheral, paresthesia, peripheral sensory neuropathy, dysaesthesia, hypoaesthesia
Rash	Rash, rash maculopapular, rash papular
Sleep disorder	Insomnia
Stomatitis	Stomatitis, mouth ulceration
Tachycardia	Sinus tachycardia
Thrombocytopenia	Platelet count decreased, thrombocytopenia
Thrombosis	Deep vein thrombosis
Viral infectious disorders	Includes HLGT of Viral infectious disorders, SARS-CoV-2 positive
Visual impairment	Visual impairment, vision blurred, blindness
*Arthralgia is not included in the GT musculoskeletal pain.	