

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s114

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

BLA Multidisciplinary Review and Evaluation

Application Number	BLA 125276 S-114
Application Type	BLA Supplement
Applicant	Genentech
Priority or Standard	Expedited
Submit Date(s)	6/1/2017
Received Date(s)	6/1/2017
PDUFA Goal Date	12/1/2017
Division/Office	DHP/OHOP
Review Completion Date	8/28/2017
Proper Name	Tocilizumab
Trade Name	Actemra
Pharmacologic Class	Interleukin-6 (IL-6) receptor antagonist
Formulation(s)	Injection (80 mg, 200 mg, 400 mg)
Dosing Regimen	Up to 4 doses at least 8 hr apart as needed • 8 mg/kg for patients weighing $\geq$ 30 kg • 12 mg/kg for patients weighing < 30 kg
Applicant Proposed Indication(s)/Population(s)	For the treatment of patients 5 years of age and older with (b) (4) severe or life-threatening cytokine release syndrome
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	For the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older

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DHOT=Division of Hematology Oncology Toxicology

DHP DDS=Division of Hematology Products Deputy Director for Safety

OBP=Office of Biologics Products

OPDP=Office of Prescription Drug Promotion

DMEPA=Division of Medication Error Prevention and Analysis

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Glossary

AACR	American Association for Cancer Research
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AERS	Adverse Event Reporting System
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ASH	American Society of Hematology
AST	aspartate aminotransferase
BID	twice a day
BiTE	bispecific T-cell receptor-engaging
BLA	Biologics License Application
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAR	chimeric antigen receptor
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDS	Core Data Sheet
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHOP	Children's Hospital of Philadelphia
CI	confidence interval
CLL	chronic lymphocytic leukemia
C _{max}	maximum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRI	complete remission with incomplete blood count recovery
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CRT	clinical review template
CS	corticosteroids

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CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
CTL019	Tsagenlecleucel-T (Novartis Pharmaceuticals)
DHOT	Division of Hematology Oncology Toxicology
DLBCL	diffuse large B cell lymphoma
DMC	data monitoring committee
DoR	duration of remission
ECG	electrocardiogram
eCTD	electronic common technical document
EFS	event-free survival
EMA	European Medicines Agency
ETASU	elements to assure safe use
ETN	etanercept
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FFP	fresh frozen plasma
GCA	giant cell arteritis
GCP	good clinical practice
GeMCRIS	Genetic Modification Clinical Research Information System
GRMP	good review management practice
HLH	hemophagocytic lymphohistiocytosis
ICH	International Conference on Harmonization
IND	Investigational New Drug
IL-1	interleukin-1
IL-6	interleukin 6
IL-6R	interleukin 6 receptor
INF- γ	interferon-gamma
IQR	interquartile range
IRB	institutional review board
IRC	Independent Review Committee
ISE	integrated summary of effectiveness
IRR	infusion-related reaction
ISS	integrated summary of safety
IRT	interdisciplinary Review Team
ITT	intent to treat
IV	intravenous
KTE-C19	axicabtagene ciloleucel (Kite Pharma, Inc.)
LD	lymphodepleting
LDH	lactate dehydrogenase
LFT	liver function tests

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MAED	MedDRA Adverse Events Diagnostic
MAS	macrophage activation syndrome
MCL	mantle cell lymphoma
MedDRA	medical dictionary for regulatory activities
mIL-6R	membrane-bound interleukin 6 receptor
mITT	modified intent to treat
MRD	minimal residual disease
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NHL	non-Hodgkin's lymphoma
NIH	National Institutes of Health
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall remission rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PGS	Penn Grading Scale
PBRER	Periodic Benefit-Risk Evaluation Report PD pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
pJIA	polyarticular juvenile idiopathic arthritis
PMBCL	primary mediastinal B cell lymphoma
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QTc	corrected QT interval
qxw	once every x weeks
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy SAE serious adverse event
r/r	relapsed or refractory
SAP	statistical analysis plan
sBLA	Supplemental Biologics License Application
SC	subcutaneous

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SCT	stem cell transplant
SGE	special government employee
sIL-6R	soluble interleukin 6 receptor
sJIA	systemic juvenile idiopathic arthritis
SMQN	Standardized MedDRA Query Narrow
SOC	standard of care
STX	siltuximab
TCZ	tocilizumab
TEAE	treatment emergent adverse event
TFL	transformed follicular lymphoma
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
UPENN	University of Pennsylvania
USPI	United States Prescribing Information
USP	United States Pharmacopoeia

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1 Executive Summary

1.1. Product Introduction

Trade Name:	Actemra
Proper Name:	Tocilizumab
Dosage Forms:	Injection (80 mg, 200 mg, 400 mg)
Therapeutic Class:	Immunosuppressant
Chemical Class:	Recombinant humanized monoclonal antibody
Pharmacologic Class:	Interleukin-6 (IL-6) receptor antagonist
Mechanism of Action:	Binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and inhibits IL-6-mediated signaling through these receptors.

BLA 125276 S-114 was submitted to support the proposed indication “for treatment of patients 5 years of age and older with (b) (4) severe or life-threatening cytokine release syndrome.”

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of tocilizumab under 21 CFR 601 for the indication “for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older.” The recommended tocilizumab dose is 8 mg/kg for patients ≥ 30 kg and 12 mg/kg for patients < 30 kg for up to 4 doses at least 8 hours apart with or without corticosteroids.

The recommendation is based on the finding in a retrospective data analysis that 69% of patients with CAR T cell-induced severe or life-threatening cytokine release syndrome (CRS) had resolution of fever and without need for vasopressors within 14 days of 1 or 2 doses of tocilizumab. Further study is required to confirm the safety of tocilizumab in the intended population.

All clinical data to support the efficacy of tocilizumab for the proposed indication were incorporated by reference to BLA 125643 for KTE-C19 and to BLA 125646 for CTL019. KTE-C19 and CTL019 are CAR T-cell products that target CD19, and the data were from clinical trials using these products for treatment of patients with CD19-positive hematological malignancies.

Since case ascertainment, grading and treatment differed by product but were similar across trials for each product itself, data were pooled only at the CAR T-cell product level. Evaluable patients had been treated with tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first

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episode of CRS was included in the analysis. The endpoint used to assess effectiveness was response, defined as being afebrile and off pressors for at least 24 hours within 14 days of the first dose of tocilizumab (maximum up to 2 doses) and without use of additional treatment other than corticosteroids. All results were reported descriptively, and there was no inferential testing planned.

The analysis cohort for the CTL019 product included 24 males and 21 females (total 45 patients) of median age 12 years (range, 3-23 years); 82% were Caucasian. The median time from start of CRS to first dose of tocilizumab was 4 days (range, 0-18 days). Thirty-one patients (69%; 95% CI: 53%-82%) achieved a response. The median time to response was 4 days (range, 1-12 days).

The analysis cohort for the KTE-C19 product included 10 males and 5 females (total 15 patients) of median age 60 years (range, 9-75 years); 87% were Caucasian. The median time from start of CRS to first dose of tocilizumab was 3 days (range, 0-14 days). Eight patients (53%; 95% CI: 30%-75%) achieved a response. The median time to response was 4.5 days (range, 2-7 days).

There is some concern that in the absence of a randomized trial or a well-characterized historical control, it is difficult to interpret the results of a retrospective review of a treated cohort. In view of the serious nature of the disease, the rapid effects on an objective early endpoint such as vital signs as reported in the literature provide substantial supporting evidence. At this point, there is insufficient equipoise for a randomized trial comparing tocilizumab to supportive care alone.

It is concluded that the high rate of response to tocilizumab for the CTL019 cohort with most responses occurring rapidly in addition to the published reports constitutes substantial evidence of effectiveness for tocilizumab in the treatment of CAR T cell-induced severe or life-threatening CRS. The KTE-C19 cohort is quite small, but the results in that cohort are confirmatory. Although the study cohorts included patients only down to the age of 3 years, the pathogenesis of CRS and the mechanism of action of tocilizumab are age-independent, so the efficacy conclusion can be extrapolated to all age groups.

1.3. Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Severe or life-threatening CRS requires advanced supportive measures. - Fatal cases have been reported.	This category of CRS is or severe or life-threatening by definition.
Current Treatment Options	Treatment with high-dose corticosteroids accelerates some responses at the cost of eliminating the efficacy of the CAR T cells.	There is a need for an effective agent to ameliorate CRS without affecting the potency of the CAR T cells.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• A retrospective cohort analysis was conducted for patients treated on clinical trials of 2 CAR T-cell products. • For the patients treated with the CTL019 product, 69% (95% CI: 53%-82%) achieved a response. • For the patients treated with the KTE-C19 product, 53%; 95% CI: 30%-75% achieved a response.	There is substantial evidence of efficacy for tocilizumab for treatment of severe or life-threatening CRS.
Risk	• The adverse reaction profile of tocilizumab is well-established in multiple intended populations. • There were no adverse reactions reported in patients treated for CRS that were attributed to tocilizumab. • The clinical trials did not collect safety data prospectively for tocilizumab specifically. • The pharmacometrics analysis suggested that up to 4 doses every 8 hours in patients with CRS would not exceed known safe exposure.	Based on available evidence, the risks of use of tocilizumab are acceptable for the intended population, but prospectively-collected data would be useful to confirm this conclusion.
Risk Management	• There is potential for toxicity if the exposure exceeds the limits identified as safe by pharmacometrics.	The limits for dosing for treatment of CRS should be explicit in labeling.

Patients with severe or life-threatening CAR T cell-induced CRS may require advanced life support, including a protracted course of vasopressors and mechanical ventilation. CRS of this severity may progress to a fatal outcome. The results of the retrospective cohort analyses showed that a substantial proportion of patients could be afebrile and off pressors relatively quickly after 1 or 2 doses of tocilizumab. One cited advantage of using tocilizumab rather than corticosteroids as first line therapy for severe CRS is the potential to delay or avoid the lympholytic action of corticosteroids and abrogation of the efficacy of CAR T cells.

The safety profile of the recommended individual doses is well-established in other intended populations down to the age of 2 years. The pharmacometrics analysis showed that patients with CRS had a faster clearance of tocilizumab than other patient populations, and simulations showed that exposure would be safe with up to 4 doses at least 8 hours apart for in patients with CRS. There were no reports of adverse reactions to tocilizumab in the patients treated for CRS, but since the safety data were not collected prospectively in relation to tocilizumab treatment, there remains some concern. This concern can be allayed by a postmarketing study.

Despite the unknowns, the seriousness of the CRS in the setting of a potentially curative therapy for cancer warrants an aggressive supportive care provided in as safe a manner as possible. Hence, the known risks of using tocilizumab appear to be outweighed by the potential benefit for patients with severe or life-threatening CAR T cell-induced CRS.

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

Cytokine release syndrome (CRS) has been identified as a significant on-target off-tumor side-effect of chimeric antigen receptor (CAR) T-cell therapies (Locke, Neelapu et al. 2017) (Grupp 2016, Fitzgerald, Weiss et al. 2017). The reported incidence of CRS following CAR T-cell therapy ranges from 50-100%, with 13-48% of patients experiencing severe or life-threatening CRS (Lee, Gardner et al. 2014) (Brudno and Kochenderfer 2016) (Frey and Porter 2016). Characteristics include fever, fatigue, hypotension, tachycardia, nausea, capillary leak, and multi-organ (cardiac, pulmonary, renal, hepatic) dysfunction.

The symptom complex in CRS results from the effects of cytokines released by immune effector and/or target cells. Inflammatory cytokines are elevated, particularly of note interleukin-6 (IL-6) (Teachey, Lacey et al. 2016). Severity of symptoms may be correlated with concentration-time exposure to the inflammatory cytokines (Kochenderfer, Dudley et al. 2012).

The natural history of CRS is not well characterized due to the rapid evolution of dose and schedule for CAR T cells. During the initial clinical experience, there was fatal case reported (Morgan, Yang et al. 2010). A 39 year-old female patient with colon cancer died 5 days after CAR T cell treatment with severe cytokine storm (Morgan, Yang et al. 2010). Multiple approaches were immediately instituted to reduce the risk of CRS, including use of low cell doses or a split-dosing schedule (Kalos, Levine et al. 2011). These approaches have mitigated some but not all of the risk of CRS.

There are multiple grading systems used to categorize patients with CRS, including the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), the Penn Grading Scale (Porter, Hwang et al. 2015), and the Lee Grading Scale (Lee, Gardner et al. 2014). The criteria for severe or life-threatening differ with regard to the categorization at which low- or high-dose vasopressors are used, but in all scales, the severe and life-threatening grades require advanced supportive care.

The severe and life-threatening form of CRS is a medical emergency that can result in significant morbidity or mortality. Treatment is directed at symptoms, for example, by administering analgesics for headache, vasopressors and IV fluids for hypotension, and supportive care with oxygen, and using intubation/mechanical ventilation for respiratory distress. High-dose corticosteroids have been used to help manage toxicity in some cases, but there is potential for corticosteroids to block T-cell activation, function, and proliferation, and therefore reduce the clinical effectiveness of the CAR T-cells (Teachey, Lacey et al. 2016). With supportive care alone, the course is generally protracted, requiring weeks for recovery from multi-organ injury.

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2.2 Analysis of Current Treatment Options

There are currently no FDA-approved drugs for treatment of cytokine release syndrome.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

ACTEMRA® (tocilizumab) has been marketed in the US as an approved product for treatment of rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (PJIA) and systemic juvenile idiopathic arthritis (SJIA) by Genentech.

(b) (4) vials of ACTEMRA for intravenous administration include: 80 mg per 4 mL; 200 mg per 10 mL; and 400 mg per 20 mL. In addition, ACTEMRA prefilled syringe (PFS) for subcutaneous administration include single use PFS providing 162 mg of ACTEMRA in 0.9 mL.

The US Prescribing information for tocilizumab includes a boxed warning for the risk of serious infections, including tuberculosis. There are additional warnings for risks of gastrointestinal perforations, neutropenia, thrombocytopenia, lipid abnormalities, elevated transaminases, immunosuppression, hypersensitivity reactions, including anaphylaxis, demyelinating disorders.

The most common adverse reactions (incidence of at least 5%) listed are upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions.

3.2 Summary of Presubmission/Submission Regulatory Activity

BLA 125276 supplemental 114 for ACTEMRA® (tocilizumab) was submitted on 06/01/2017 for the indication “treatment of patients with (b) (4) severe or life-threatening cytokine release syndrome.”

Correspondence between the Sponsor and the FDA started 2015 related to the use of ACTEMRA® (tocilizumab) for the treatment of CRS and a potential regulatory pathway for registration. The key events in the US presubmission regulatory activities include:

03/24/2016: FDA enquired about whether the Sponsor had any registration plans for a CRS indication, given the off-label use occurring which would be relevant to several oncology immunotherapies.

09/09/2016: Type C meeting held under pre-Investigational New Drug Application (PIND) 125952:

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- FDA recommended that a submission based on literature would not be sufficient for a marketing application and that a prospective trial would be needed for a BLA supplement for treatment of CRS. FDA indicated support for ongoing discussions as the retrospective and prospective protocols are developed and recommended that the Sponsor request formal meetings with brief background material and specific questions for complicated or critical protocol design issues.

04/19/2017: Type A meeting held under PIND 125952:

- FDA enquired about the Sponsor's ongoing discussions with Kite Pharma and potentially leveraging the available data from their CAR T-cell therapy, KTE-C19, for the purposes of updating the tocilizumab label for CRS and recommended that the Sponsor pursue a letter of authorization granting FDA access to analyze the KTE-C19 data under review for tocilizumab in CRS.

- FDA also enquired as to whether the Sponsor has had any discussions with Novartis regarding their CAR T-cell therapy, CTL019, as the data is also under review at FDA and encouraged the Sponsor to discuss a potential letter of authorization for FDA to analyze the CTL019 data under review for tocilizumab in CRS.

- FDA suggested the high-level proposal for a streamlined license application based on a comprehensive literature review and publications supporting the use of tocilizumab for the treatment of severe or life-threatening CRS, in addition to the potential letters of authorization from Kite Pharma and Novartis allowing FDA to analyze the data generated in the trials of their CAR T-cell therapies and presented in the respective BLAs for this purpose.

05/12/2017: Submission of an application for Orphan Drug Designation for tocilizumab in the treatment of patients with severe or life-threatening CRS to the FDA's Office for Orphan Products Development.

06/01/2017: This BLA 125276 supplement (S-114) was received in Electronic Common Technical Document (eCTD) format. The submission was found to be technically complete for review.

08/01/2017: FDA designated tocilizumab as Orphan Drug for the treatment of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome.

In addition, outside of the US, the Sponsor's co-development partner in Japan, Chugai Pharmaceutical Company Ltd (a member of the Roche group), is investigating the efficacy of tocilizumab as treatment for CRS caused by CAR T-cell therapy.

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

4.1 Office of Scientific Investigations (OSI)

There were no clinical site audits conducted by the Office of Scientific Investigations for review of this BLA supplement. See the reviews of BLA 125646 and BLA 125643 for audits of the clinical trials contributing data to support the proposed indication.

4.2. Product Quality

No new product quality data were submitted for review in this supplement. The sponsor's request categorical exclusion under 21 CFR 25.31 (c) was found to be acceptable.

4.3 Devices and Companion Diagnostic Issues

There are no companion diagnostic devices required for the proposed use of tocilizumab.

5 Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted for review in this supplement.

Donna Przepiorka, MD, PhD
Cross-Discipline Team Leader

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6 Clinical Pharmacology

6.1 Executive Summary

The key review question focuses on the appropriateness of the dose for the administration of ACTEMRA in adult and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS).

The Office of Clinical Pharmacology has reviewed the information contained in this Efficacy Supplement of BLA 125276. This supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments								
Evidence of effectiveness	Five trials under BLA 125646 and four trials under BLA 125643 provide primary evidence.								
General Dosing instructions	Use only the intravenous route for treatment of CRS. The recommended dose of ACTEMRA for treatment of CRS given as a 60-minute intravenous (b) (4) infusion is: <table><tr><th colspan="2">Recommended Intravenous CRS Dosage</th></tr><tr><td>Patients less than 30 kg weight</td><td>12 mg per kg</td></tr><tr><td>Patients at or above 30 kg weight</td><td>8 mg per kg</td></tr><tr><td colspan="2">Alone or in combination with corticosteroids.</td></tr></table> - If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of ACTEMRA may be administered. The interval between consecutive doses should be at least 8 hours. - Subcutaneous administration is not approved for CRS. The recommended dosing regimen is effective and appears to be safe.	Recommended Intravenous CRS Dosage		Patients less than 30 kg weight	12 mg per kg	Patients at or above 30 kg weight	8 mg per kg	Alone or in combination with corticosteroids.	
Recommended Intravenous CRS Dosage									
Patients less than 30 kg weight	12 mg per kg								
Patients at or above 30 kg weight	8 mg per kg								
Alone or in combination with corticosteroids.									

There is no Post-Marketing Requirement (PMR) or Post-Marketing Commitment (PMC) from clinical pharmacology perspective.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist. It inhibits IL-6-mediated signaling through binding to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). ACTEMRA (tocilizumab) is approved for treatment of rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (PJIA), or systemic juvenile idiopathic arthritis (SJIA). For brevity, only information related to the current supplement is summarized.

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Based on preliminary sparse PK data from Novartis Trial ELIANA (CTL019B2202), the geometric mean (coefficient of variation, % CV) C_{max} in patients with CAR T cell-induced severe or life-threatening CRS was 99.5 µg/mL (36.8%) following the first IV infusion dose ranging from 6.94 mg/kg to 12 mg/kg (n = 27) and 160.7 µg/mL (113.8%) following the second dose ranging from 8 mg/kg to 12 mg/kg (n = 8).

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The Sponsor proposes a dose of ACTEMRA 12 mg per kg for patients less than 30 kg weight or 8 mg per kg for patients at or over 30 kg weight via intravenous infusion alone or with high dose corticosteroids. (b) (4)

However, reviewers recommended the following dosage for patients with CAR T cell-induced severe or life-threatening CRS based on our own simulation results:

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids.	

If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of ACTEMRA may be administered. The interval between consecutive doses should be at least 8 hours.

Therapeutic Individualization

There is no additional data to support therapeutic individualization in patients with CRS. Dose adjustment in specific populations with CRS should follow the current recommendations in the labeling.

Outstanding Issues

There are no outstanding issues at this time.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacokinetics of tocilizumab has been well characterized in patients with rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis

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(PJIA), or systemic juvenile idiopathic arthritis (SJIA). Please refer to the current labeling and the clinical pharmacology reviews in the following links for more detailed information:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s111,125472s023lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000ClinPharmR.pdf

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM259750.pdf>

PK data was only available from a single clinical trial. Based on preliminary 131 PK observations from 27 patients in Novartis Trial ELIANA (CTL019B2202), the geometric mean (% CV) of C_{max} in patients with CAR T cell-induced severe or life-threatening CRS was 99.5 $\mu\text{g/mL}$ (36.8%) following the first IV infusion dose ranging from 6.94 mg/kg to 12 mg/kg ($n = 27$) and 160.7 $\mu\text{g/mL}$ (113.8%) following the second dose ranging from 8 mg/kg to 12 mg/kg ($n = 8$). PK data is insufficient to reliably generate other PK parameters for tocilizumab due to the sparse PK sampling schedule in Trial ELIANA.

6.3.2 Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dose level of 12 mg/kg (< 30 kg weight) or 8 mg/kg (≥ 30 kg weight) is appropriate for adults and pediatric 2 years of age and older with CAR T cell-induced severe or life-threatening CRS. The dose demonstrated effectiveness in patients with CRS based on the results from five Novartis trials (CTL019A2201, CTL019B2101J, CTL019B2102J, CTL019B2202 and CTL019B2205J) under BLA 125646 and four Kite Pharma trials (Zuma-1, Zuma-2, Zuma-3 and Zuma-4) under BLA 125643. (b) (4)

we recommend that up to 3 additional doses of ACTEMRA may be administered with a dosing interval of at least 8 hours if no clinical improvement in the signs and symptoms of CRS occurs after the first dose. The simulated tocilizumab concentrations after four IV infusion doses every 8 hours will generally be below the highest C_{max} observed for tocilizumab and therefore the safety profile will likely be consistent with previous clinical experience.

Efficacy

As there were no specific primary endpoints for the efficacy of tocilizumab for the treatment of CRS in the BLA 125646 and BLA 125643, resolution response and response rate of Grade 3-4 first CRS to one or two dose(s) of tocilizumab within 14 days after the first infusion of tocilizumab at 8 mg/kg (or 12 mg/kg for patient weight < 30 kg) were used to assess the effectiveness of tocilizumab. Thirty-one of 45 patients (68.9%; 95% CI: 53.4%, 81.8%) in five Novartis trials under BLA 125646 and 8 of 15 patients (53.3%; 95% CI: 30.1%, 75.2%) in four Kite Pharma trials under BLA 125463 achieved a response of Grade 3-4 first CRS to one or two

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dose(s) of tocilizumab within 14 days after the first infusion (**Table 1**). Due to narrow exposure range derived from only one dose level with limited sample size ($n = 27$) in Novartis Trial ELIANA, definitive exposure-efficacy data cannot be conducted.

Table 1: Resolution Responses and Response Rates of Grade 3-4 First CRS to One or Two Dose(s) of Tocilizumab within 14 Days after the First Infusion of Tocilizumab at 8 mg/kg (or 12 mg/kg for Patient Weighted < 30 kg) in BLAs 125646 and 125643.

BLA	No. of trials	Responders	Response rate % (95% CI)
125646	5	31/45	68.9% (53.4%, 81.8%)
125643	4	8/15	53.3% (30.1%, 75.2%)

Source: Reviewers' analysis.

Safety

There were no reports of deaths attributed to tocilizumab in the patients with CRS.

Appropriateness of proposed dosage regimen

The majority (117/132, 88.6%) of the patients received one or two dose(s) of tocilizumab to manage the CAR T cell-induced severe or life-threatening CRS in 5 Novartis trials under BLA 125646 and 4 Kite Pharma trials under BLA 125643 (**Table 2**). For those 52 (39.4%) patients who took two or more doses of tocilizumab, 42 (31.8%) patients took tocilizumab on different days; only 6 (4.5%) patients took 2 doses and 3 (2.3%) patients took 3 doses within 24 hours.

(b) (4)

As there was no detailed safety data available in patients with CRS in all 9 trials, population PK modeling and simulation was used to evaluate the appropriateness of the Genentech proposed dosage regimen for tocilizumab in patients with CRS. The population PK model developed in pediatric patients with SJIA over-predicted the PK data from patients with CRS, thus the population PK model was refined with higher linear clearance (CL) of 0.50 L/day (relative standard error, RSE = 10.8%) and volume of distribution in central compartment (V_c) of 1.8 L (RSE = 11.2%) using PK data from patients with CRS (see details in [Section 13.4.3](#) for more information). Simulations were thereafter conducted using the refined PK model to simulate the PK profiles of tocilizumab in patients with CRS after four doses of tocilizumab every 24 hours, 12 hours or 8 hours (**Figure 1**). As the maximum tolerated dose was not reached in previous trials for tocilizumab, the “safety threshold” from previous clinical experience was used to determine the acceptable dosage regimen for patients with CRS. The maximum observed C_{max} at steady state was 547 $\mu\text{g/mL}$ and no trend was observed towards increased incidence in AEs or SAEs with increasing tocilizumab exposure in 122 patients with SJIA in Genentech Trial WA18221. The maximum observed C_{max} was 649 $\mu\text{g/mL}$ in five healthy subjects

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after a single dose of 28 mg/kg tocilizumab in Genentech Trial BP19461, and it was generally well tolerated with only absolute neutrophil counts decreasing to the nadir 3-5 days following tocilizumab administration. Given the severity and life-threatening nature of CAR T cell-induced CRS and available treatment to manage neutropenia (e.g. G-CSF products), the observed maximum concentration of 649 µg/mL was used as a “safety threshold” to assess and select the dosage regimen for tocilizumab in patients with CRS. The simulation results showed scenarios where tocilizumab was administered every 24 hours, 12 hours or 8 hours. The simulated tocilizumab concentrations after four IV infusion doses were generally below this “safety threshold”. Therefore, a total of four tocilizumab doses of 12 mg/kg (<30 kg weight) or 8 mg/kg (≥30 kg weight) with a dosing interval of at least 8 hours is acceptable for adult and pediatric patients 2 years of age and older with CAR T cell-induced severe or life-threatening CRS.

Table 2: Number of Total Tocilizumab Doses Administered in Patients with CAR T cell-induced Severe or Life-threatening CRS in 5 Novartis Trials under BLA 125646 and 4 Kite Pharma Trials under BLA 125643.

No. of tocilizumab doses	No. (%) of patients in 5 trials under BLA 125646	No. (%) of patients in 4 trials under BLA 125643	All
1	34 (58.6%)	48 (63.2%)	82 (62.1%)
2	17 (29.3%)	18 (23.7%)	35 (26.5%)
3	6 (10.4%)	4 (5.3%)	10 (7.6%)
≥4	1 (1.7%)	6 (7.8%)	7 (5.3%)

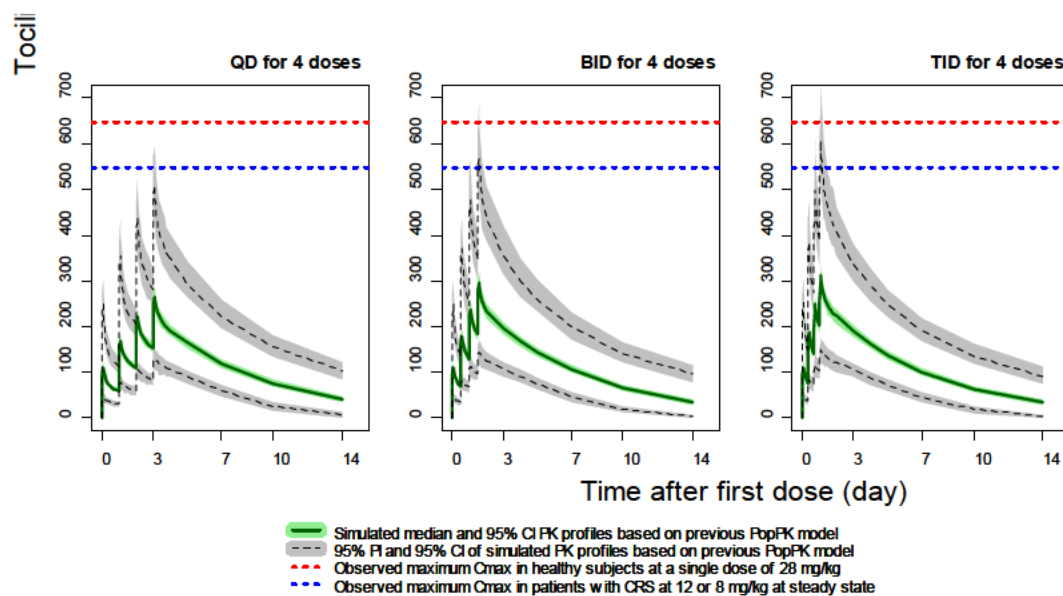


Figure 1: Simulated 2.5th, 50th and 97.5th Percentiles and Corresponding 95% Confidence Intervals of the Tocilizumab PK Profiles in Patients with CAR T cell-induced Severe or Life-threatening CRS after Four doses Every 24 Hours (Left Panel), 12 Hours (Middle Panel) or 8 Hours (Right Panel) in Patients with CRS.

Source: Reviewers' analysis.

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7 Statistical and Clinical and Evaluation

7.1 Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies/Trials

Table 3: Table of Clinical Trials

Trials / Status	Design	Population	Primary Endpoint
BLA 125646 including CTL019			
Protocol CCTL019B2202 (ELIANA)	Phase 2, single arm, international, multicenter trial to determine the efficacy and safety of CTL019	Pediatric and young adult patients with relapsed and refractory B-cell ALL	Primary: IRC-assessed ORR (CR + CRi) Secondary: MRD, DoR, BOR, EFS, OS, safety, PRO
Protocol CCTL019B2205J	Phase 2, single arm, US multicenter trial to determine the efficacy and safety of CTL019	Pediatric patients with relapsed and refractory B-cell ALL	Primary: IRC-assessed ORR Secondary: MRD, DoR, BOR, EFS, OS, safety
Protocol CCTL019B2101J	Phase 1/2a, study of autologous T cells expressing attached to TCR ζ and 4-1BB signaling domains	Patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma	Primary: Safety, feasibility of manufacture, and persistence Secondary: IRC-assessed ORR
Protocol CCTL019A2101	Phase 1/2, autologous T cells expressing anti-CD19 CAR	Patient with relapsed or refractory CD19+ chronic lymphocytic leukemia	Primary: Complete response by 3 months (Stage 1 Report) Secondary: safety, additional efficacy parameters
Protocol CCTL019B2102J	Phase 1 pilot study, autologous T cells expressing anti-CD19 attached to TCR-zeta and 4-1BB signaling	Patient with resistant or refractory CD19+ leukemia and lymphoma	Primary: Safety and feasibility Secondary: anti-tumor activity in vivo, survival and response rates

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Table 3: Table of Clinical Trials

Trials / Status	Design	Population	Primary Endpoint
BLA 125643 including KTE-C19			
Protocol KTE-C19-101 (ZUMA-1)	Phase 1/2, multi-center study of KTE-C19	Patients with refractory aggressive B-cell NHL	Primary Phase 1: Safety; Primary Phase 2: ORR Secondary: DOR, best overall response, PFS, OS
Protocol KTE-C19-102 (ZUMA-2)	No protocol has been submitted in the BLA, but the Sponsor referred to protocol in IND 16278: Phase 2 multicenter Study of KTE-C19	Patients with relapsed or refractory mantle cell lymphoma	Primary: ORR Secondary: DOR, best overall response, PFS, OS
Protocol KTE-C19-103 (ZUMA-3)	No protocol has been submitted in the BLA, but the Sponsor referred to protocol in IND 16675: Phase 1/2, multi-center study of KTE-C19	Adult Patients with relapsed or refractory B-precursor ALL	Primary Phase 1: Safety; Primary Phase 2: ORR Secondary: DOR, best overall response, PFS, OS
Protocol KTE-C19-104 (ZUMA-4)	No protocol has been submitted in the BLA; but the Sponsor referred to protocol in IND 16675: Phase 1/2, multi-center study of KTE-C19	Pediatric and Adolescent patients with relapsed or refractory B-precursor ALL	Primary Phase 1: Safety; Primary Phase 2: ORR Secondary: DOR, best overall response, PFS, OS
Source: BLA 125646 and BLA 125643 eCTD Module 5, BLA 125646 Sponsor's responses on 6/28/2017 and BLA 125643 Sponsor's responses on 7/10/2017 to FDA information requests. Abbreviations: ALL, Acute lymphoblastic leukemia; CAR, chimeric antigen receptor; r/r, Relapsed or refractory; CR, Complete remission; CRi, Complete remission with incomplete blood count recovery; BOR, Best overall response; DoR, Duration of remission; EFS Event-free survival; IRC, Independent Review Committee; MRD, Minimal residual disease; ORR, Overall remission rate; OS, Overall survival; PRO, Patient-reported outcomes; NHL, Non-Hodgkin lymphoma ; DLBCL, Diffuse large B cell lymphoma; PMBCL, Primary mediastinal B cell lymphoma; TFL, Transformed follicular lymphoma; MCL, Mantle cell lymphoma.			

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7.1.2. Review Strategy

The key materials used for this review of efficacy and safety include:

- BLA 125276 (tocilizumab)
- BLA 125643 (axicabtagene ciloleucel) from Kite Pharma, Inc. (Kite)
- BLA 125646 (tisagenlecleucel) from Novartis Pharmaceuticals Corporation (Novartis)
- Published literature

BLA 125276 provided the safety data for the proposed dosing as studied extensively in different intended populations. S-114 also included a comprehensive literature review on the use of tocilizumab for treatment of CRS.

BLA 125643 included individual data files for 5 trials. (b) (4)

(b) (4) their analyses of use of tocilizumab was (b) (4) Zuma-1, Zuma-2, Zuma-3 and Zuma-4, (b) (4) (BLA 125643 Response to Information Request dated 7/10/2017). The CMC reviewer for BLA 125643 indicated that only the product from Zuma-1 is considered axicabtagene ciloleucel, and the other 3 trials utilize the related KTE-C19 (email 7/20/2017). For the purposes of this review, the data are pooled from the 4 Kite trials under product KTE-C19.

BLA 125646 included individual data files for 5 trials. The CMC reviewer for BLA 125646 indicated that only the product for CCTL019B2202 is considered tisagenlecleucel, and the other 4 trials utilize the related CTL019 (email 7/21/2017). For the purposes of this review, the data are pooled the 5 Novartis trials under product CTL019.

Data Sources

This review used custom integrated data files provided by Kite and Novartis in their respective BLAs. These data included tociae.xpt received 08/11/2017 and tociadmn.xpt received 08/21/2017 from Kite for BLA 125643, and adcmcrs.xpt and adcrs.xpt received 07/07/2017 from Novartis for BLA 125646.

Data and Analysis Quality

The integrated data files as dated and described above were considered reviewable. The limitations of the data files with regard to the assessments of efficacy and safety are discussed in Sections 7.3.1 and 7.4.1, respectively, below.

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7.2 Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. CTL019 - Retrospective Analysis of Data

CTL019 - STUDY DESIGN

Description of Trials

This study used the data from the 5 trials submitted in BLA 125646 as described in Table 3 above.

(1) Protocol CCTL019B2202 (ELIANA)

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

The key inclusion criteria included relapsed or refractory pediatric (3-21 years at screening) B-cell ALL. The study sites included 25 centers internationally. The first patient was enrolled on April 8, 2015; and the last patient was enrolled for this review and analysis on August 17, 2016. Data cut-off for efficacy analysis was November 23, 2016. A total of 81 patients were enrolled, 62 were treated with CTL019, and 53 were reported as having CRS.

(2) Protocol CCTL019B2205J

A phase 2, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia

The key inclusion criteria included relapsed or refractory pediatric (3-25 years at screening) B-cell ALL. The study sites included 9 centers in US. The first patient was enrolled on August 14, 2014; and the last patient was enrolled for this review and analysis on June 10, 2015. Data cut-off for efficacy analysis was February 01, 2016. A total of 35 patients were enrolled, 29 were treated with CTL019, and 26 were reported as having CRS.

(3) Protocol CCTL019B2101J

Pilot study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR ζ and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma

The key inclusion criteria included resistant or refractory pediatric (1-24 years at screening) CD19+ leukemia and lymphoma. The trial was conducted at a single site. The first patient was enrolled on March 15, 2012; and the last patient was enrolled for this review and analysis on July 22, 2015. Data cut-off for efficacy analysis was November 30, 2015. A total of 71 patients were enrolled, 60 were treated with CTL019, and 53 were reported as having CRS.

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(4) Protocol CCTL019A2101

Dose optimization trial of autologous T cells engineered to express anti-CD19 chimeric antigen receptor in patients with relapsed or refractory CD19+ chronic lymphocytic leukemia

The key inclusion criteria included relapsed or refractory adult (age ≥ 18 years at screening) CD19+ chronic lymphocytic leukemia. The trial was conducted at a single site. The first patient was enrolled on January 02, 2013; and the last patient was enrolled for this review and analysis on June 30, 2014. Data cut-off for efficacy analysis was September 15, 2015. A total of 30 patients were enrolled, 28 were treated with CTL019, and 10 were reported as having CRS.

(5) Protocol CCTL019B2102J

Pilot study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR-zeta and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma

The key inclusion criteria included resistant or refractory adult (age > 18 years at screening) CD19+ leukemia and lymphoma. The trial was conducted at a single site. The first patient was enrolled on March 17, 2010; and the last patient was enrolled for this review and analysis on August 07, 2013. Data cut-off for efficacy analysis was July 06, 2015. A total of 26 patients were enrolled, 20 were treated with CTL019, and 14 were reported as having CRS.

The protocols provided detailed criteria for grading CRS, treatment algorithm with criteria for CRS management. For each trial, the eCTD location of criteria for grading CRS and instructions for use of tocilizumab for treatment of CRS is provided in Table 4 below.

Table 4: CTL019 - Location of CRS Grading Criteria and Tocilizumab Use Instructions

Study	Criteria for grading CRS (protocol page number in clinical study report (CSR))	Instructions for use of tocilizumab (protocol page number in clinical study report)
CTL019B2202	Pgs. 3520 [Study B2202 CSR]	Pgs. 3514, 3517-3520 [Study B2202 CSR]
CTL019B2205J	Pgs. 2513 [Study B2205J CSR]	Pgs. 2508, 2510-2512 [Study B2205J CSR]
CTL019B2101J	Pgs. 3406-3408 [Study B2101J CSR]	Pgs. 3604-3408 [Study B2101J CSR]
CTL019A2101	Pgs. 2364-2366 [Study A2101 CSR]	Pgs. 2374-2376 [Study A2101 CSR]
CTL019B2102J	Pgs. 1850-1853 [Study B2102J CSR]	Pgs. 1863-1865 [Study B2102J CSR]

Source: BLA 125646 Sponsor's responses on 6/28/2017 to FDA information requests.

Abbreviations: CRS, Cytokine release syndrome; CSR, Clinical study report.

Identification and Grading of CRS

Novartis indicated that patients with CRS were identified by the data element from the trial case report form (BLA 125646 Response to Information Request date 8/11/2017). Grading of CRS utilized a modified CTCAE known as the Penn Grading Scale (Table 5). The only difference in the grading scales across trials was that Grade 2 in CTL019B2101J did not include patients hospitalized for treatment of any signs or symptoms of CRS (Table 4 in Protocol CTL019B2101J).

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Table 5: CTL019 - Penn Grading Scale for CRS

Grade	Severity	Description
Grade 1	Mild	Treated with supportive care such as antipyretics and anti-emetics.
Grade 2	Moderate	Requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests [LFTs]) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.
Grade 3	Severe	Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids ¹ or low dose pressors, ² coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.
Grade 4	Life-threatening	Life-threatening complications such as hypotension requiring high dose pressors or hypoxia requiring mechanical ventilation.

¹Defined as multiple fluid boluses for blood pressure support

²Definition of high-dose vasopressor

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

Source: Protocol CTL019B2202 v.4 Table 6-1 and 6-2.

Planned Treatment of CRS

Table 6 shows the algorithm used for treatment of CRS. The only major difference in the treatment algorithm across trials was that the recommended tocilizumab dose was 8 mg/kg in Protocol CTL019A2201, 4 mg/kg in Protocol CTL019B2102J, and based on weight > or < 30 kg as indicated in Table 6 in the remainder of the trials.

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Table 6: CTL019 - CRS Treatment Algorithm

Prodromal syndrome: low grade fevers, fatigue, anorexia (hours to days)
Observation, rule out infection (surveillance cultures)
Antibiotics per local guidelines (febrile neutropenia)
Symptomatic support
Symptom progression: High fevers, hypoxia, mild hypotension
1st Line Management:
Oxygen, fluids, low dose vasopressor support, antipyretics
Monitor/manage complications of TLS
Further symptom progression:
- Hemodynamic instability despite intravenous fluids and moderate to "high dose" vasopressor¹ support OR - Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow Oxygen (O₂) and/or need for mechanical ventilation OR - Rapid clinical deterioration
2nd Line Management:
Tocilizumab: IV infusion over 1 hour
- Patient weight < 30 kg: 12 mg/kg i.v. - Patient weight ≥ 30 kg: 8 mg/kg i.v. (max dose 800 mg)
Hemodynamic and respiratory support
Lack of clinical improvement while awaiting tocilizumab response
3rd Line Management:
Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)
If no improvement with 1 st dose of tocilizumab within 12 to 18 hours, consider steroids (plan rapid taper after hemodynamic normalization):
2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day. As steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement
If no response to steroids within 24 hours, consider 2 nd dose of Tocilizumab (dosed as above)
Hemodynamic and respiratory support
Lack of clinical improvement while awaiting response to 3rd line management
4th Line Management:
Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)
If no response to steroids and 2 nd dose of tocilizumab within 24 hours or further clinical deterioration, consider siltuximab 11 mg/kg IV over 1 hour
Hemodynamic and respiratory support
Lack of clinical improvement while awaiting response to 4th line management
5th Line Management:
Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)
In ongoing CRS despite prior therapy, consider anti-T cell therapies such as cyclophosphamide, anti-thymocyte globulin, or alemtuzumab
Hemodynamic and respiratory support

Source: Protocol CTL019B2202 v.4 Figure 6-1

Data Analysis Plan

The primary objective of the retrospective analysis developed by the clinical review team was to characterize the resolution of severe or life-threatening CAR T cell-induced CRS after treatment with tocilizumab.

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The Efficacy Population consisted of patients with grade 3-4 first episode of CRS treated with the first dose of tocilizumab at the recommended 8 mg/kg (or 12 mg/kg for patient weight < 30 kg).

The primary endpoint was day-14 response, defined as being afebrile and off pressors for at least 24 hours within 14 days of the first dose of tocilizumab (maximum up to 2 doses) and without use of additional treatment other than corticosteroids. The date of resolution of CRS as defined was as reported by Novartis (Response to Information Request dated 6/28/2017).

Additional endpoints assessed included response at 2, 7 and 21 days from the first dose of tocilizumab, time to response for responders, and response by demographic subgroup. Additional analyses were performed in all patients who were treated with any dose of tocilizumab for CAR T cell-induced CRS at any grade. Additional exploratory analyses included response by first tocilizumab dose, number of tocilizumab doses and use of multiple doses within one day.

All results were reported descriptively. There was no inferential testing planned.

CTL019 - STUDY RESULTS

Compliance with Good Clinical Practices

Novartis reported that all CTL019 trials in BLA 125646 were conducted in compliance with Good Clinical Practice (GCP). At the time of this submission, there were no major GCP issues reported.

Financial Disclosure

Novartis provided certifications on FDA Form 3454 that there were no financial arrangements that met the requirements for disclosure for the investigators in the studies. See Section 13.2.

Results

The results of the retrospective analyses are described in Sections 7.3 and 7.4.

7.2.2 KTE-C19 - Retrospective Analysis of Data

KTE-C19 - STUDY DESIGN

This study used the data from the 4 trials submitted in BLA 125643 as described in Table 3 above.

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Description of Trials

(1) Protocol ZUMA-1:

Phase 1/2 multi-center study evaluating the safety and efficacy of KTE-C19 in patients with refractory aggressive non-Hodgkin lymphoma (NHL) (ZUMA-1)

The key inclusion criteria included adult (age > 18 years at screening) patients with refractory aggressive non-Hodgkin lymphoma. The trial was conducted at 24 centers (23 in the US and 1 center in Israel). The first patient was enrolled on April 21, 2015; and the last patient was enrolled for this review and analysis on June 29, 2016. Data cut-off for efficacy analysis was January 27, 2017. A total of 119 patients were enrolled, 108 were treated with KTE-C19, and 100 were reported as having CRS.

(2) ZUMA-2 study:

A Phase 2 multicenter study evaluating the efficacy of KTE-C19 in patients with relapsed/refractory mantle cell lymphoma (r/r MCL) (ZUMA-2)

The key inclusion criteria included adult (age > 18 years at screening) patients with relapsed/refractory mantle cell lymphoma (r/r MCL). The trial was conducted at 35 centers (in North America and Europe). A total of 24 patients were treated with KTE-C19, and 24 were reported as having CRS.

(3) ZUMA-3 study:

A Phase 1/2 multi-center study evaluating the safety and efficacy of KTE-C19 in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) (ZUMA-3)

The key inclusion criteria included adult (age > 18 years at screening) patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). The trial was conducted at multiple centers. A total of 16 patients were treated with KTE-C19, and 16 were reported as having CRS.

(4) ZUMA-4 study:

A Phase 1/2 multi-center study evaluating the safety and efficacy of KTE-C19 in pediatric and adolescent patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) (ZUMA-4)

The key inclusion criteria included pediatric and adolescent patients with r/r ALL. The trial was conducted at a single site. A total of 7 patients were treated with KTE-C19, and 7 were reported as having CRS.

The protocols provided detailed criteria for grading CRS, treatment algorithm with criteria for CRS management. For each trial, the location of criteria for grading CRS and instructions for use

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of tocilizumab for treatment of CRS is provided in Table 7 below.

Table 7: KTE-C19 - Location of CRS Grading Criteria and Tocilizumab Use Instructions

Study	Criteria for grading CRS (location in the protocol)	Instructions for use of tocilizumab (location in the protocol)
ZUMA 1 (protocol 12 Aug 2016)	Table 17, Page 51	Table 18, page 51
ZUMA 2 (protocol 23 Aug 2016)	Table 17, Page 45	Table 18, Page 46
ZUMA 3 (protocol 10 Mar 2017)	Table 18, Page 54	Table 19, Page 55
ZUMA 4 (Protocol 07 Sep 2016)	Table 15, Page 49	Table 16, Page 50

Source: BLA 125643 response on 7/10/2017 to FDA information requests

Abbreviations: CRS, Cytokine release syndrome

Identification and Grading of CRS

Kite indicated that patients with CRS were identified by a data element from the trial case report form (BLA 125643 Response to Information Request date 8/11/2017). Grading of CRS utilized the Lee Grading Scale (Lee, Gardner et al. 2014) (Table 8) across all KTE-C19 trials.

Table 8: KTE-C19 - Lee Grading Scale for CRS

Grade	Symptoms
Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement $\geq$ 40% or hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Source: BLA 125643 eCTD Module 5.3.5.1 Protocol ZUMA-1 Table 17 on page 51

Planned Treatment of CRS

Table 9 shows the algorithm used for treatment of CRS in the KTE-C19 trials. Across the trials, the dose of tocilizumab was 8 mg/kg every 4-6 hours up to a maximum of 3 doses per day.

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Table 9: KTE-C19 - CRS Treatment Algorithm

Cytokine Release Syndrome Grading assessment	Extensive co-morbidities or older age? No/Yes	Treatment
Grade 1: - Fever (defined as $\geq 38.3^{\circ}\text{C}$) - Constitutional symptoms	N/A	- Vigilant supportive care - Assess for infection - Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed
Grade 2: - Hypotension: responds to fluids or one low dose vasopressor - Hypoxia: responds to $< 40\% \text{ O}_2$ - Organ toxicity: grade 2	No	- As above for grade 1 - Monitor organ function closely Monitor with continuous cardiac telemetry and pulse oximetry
Grade 2: - Hypotension: responds to fluids or one low dose vasopressor - Hypoxia: responds to $< 40\% \text{ O}_2$ - Organ toxicity: grade 2	Yes	- As above for grade 2 - Consider tocilizumab (8mg/kg IV over 1 hr, not to exceed 800mg) $\pm$ corticosteroids (e.g., methylprednisolone 1mg/kg BID or dexamethasone 10mg q6hrs)^b
Grade 3: - Hypotension: requires multiple vasopressors or high dose vasopressors^a - Hypoxia: requires $\geq 40\% \text{ O}_2$ - Organ toxicity: grade 3 or grade 4 transaminitis	N/A	
Grade 4 - Mechanical ventilation - Organ toxicity: grade 4 excluding transaminitis	N/A	- As above for grade 2/3 - Corticosteroids (e.g., methylprednisolone 1g/day x3, followed by a rapid taper consisting of 250mg BID x2 days, 125mg BID x2 days and then 60mg BID x2 days)^b

Source: BLA 125643 eCTD Module 5.3.5.1 Protocol ZUMA-1 Table 18 on page 52

Data Analysis Plan

The primary objective of the retrospective analysis developed by the clinical review team was to characterize the resolution of severe or life-threatening CAR T cell-induced CRS after treatment with tocilizumab.

The Efficacy Population consisted of patients with grade 3-4 first episode of CRS treated with the first dose of tocilizumab at the recommended 8 mg/kg (or 12 mg/kg for patient weight < 30 kg).

The primary endpoint was day-14 response, defined as being afebrile and off pressors for at least 24 hours within 14 days of the first dose of tocilizumab (maximum up to 2 doses) and without use of additional treatment other than corticosteroids. The date of resolution of CRS

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as defined was as reported by Kite (Response to Information Request dated 8/18/2017).

Additional endpoints assessed included response at 2, 7 and 21 days from the first dose of tocilizumab, time to response for responders, and response by demographic subgroup. Additional analyses were performed in all patients who were treated with any dose of tocilizumab for CAR T cell-induced CRS at any grade. Additional exploratory analyses included response by first tocilizumab dose, number of tocilizumab doses and use of multiple doses within one day. All results were reported descriptively. There was no inferential testing planned.

KTE-C19 - STUDY RESULTS

Compliance with Good Clinical Practices

Kite reported that all KTE-C19 trials in BLA 125643 were conducted in compliance with Good Clinical Practice (GCP). At the time of this submission, there were no major GCP issues reported.

Financial Disclosure

Kite provided certifications on FDA Form 3454 that there were no financial arrangements that met the requirements for disclosure for the investigators in the studies. See Section 13.2.

Results

The results of the retrospective analyses are described in Sections 7.3 and 7.4.

7.3 Integrated Review of Effectiveness

7.3.1 Assessment of Efficacy Across Trials

Methods

The Sponsor proposed the indication “For the treatment of patients 5 years of age and older with [REDACTED] (b) (4) severe or life-threatening cytokine release syndrome.” Limited data about the outcomes of patients treated with tocilizumab for CAR T cell-induced CRS were available from 2 series of clinical trials in cross-referenced BLAs, one for the product CTL019 and the other for the product KTE-C19. Due to the differences in the patient populations, the retrospective analyses of these series were evaluated side-by-side and not pooled in the integrated assessment of effectiveness.

As measures of effectiveness, FDA considered using rapid reductions in various measures of

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vital signs, but it was not clear that such outcomes as resolution of fever alone would be a sufficient clinical benefit. Complete resolution of all signs and symptoms would likely also not be applicable, since complete resolution would require healing of damaged organs, a variable patient-dependent outcome which is not a proposed benefit of tocilizumab. Moreover, the data available was not sufficiently granular to allow for such analyses. The criteria used for the CTL019 series, being afebrile and off vasopressors for 24 hours, were considered adequate to reflect the action of tocilizumab and beneficial for the patients if no other drugs were needed, and if the response occurred in a timely fashion (e.g., within 14 days). To ensure robustness, the results of corroborating analyses would need to be consistent.

Derivation of the Analysis Populations

Data were provided for 156 patients with CRS in the series of CTL019 trials and 147 patients with CRS in the series of KTE-C19 trials (Table 10).

Table 10: Analysis Populations

Trial	Product	Patients with CRS	Patients with CRS Treated with Tocilizumab	Patients with grade 3-4 CRS Treated with the Recommended Dose of Tocilizumab
CCTL019A2201	CTL019	10	3	0
CCTL019B2101J	CTL019	53	16	14
CCTL019B2102J	CTL019	14	6	0
CCTL019B2202	CTL019	53	26	24
CCTL019B2205J	CTL019	26	7	7
<i>Total</i>	<i>CTL019</i>		<i>58^a</i>	<i>45^b</i>
KTE-C19-101	KTE-C19	100	46	8
KTE-C19-102	KTE-C19	24	13	3
KTE-C19-103	KTE-C19	16	13	2
KTE-C19-104	KTE-C19	7	4	2
<i>Total</i>	<i>KTE-C19</i>		<i>76^a</i>	<i>15^b</i>

Source: FDA analysis

^aTreated Population

^a Efficacy Population

The analysis populations derived from this data set included:

- **Treated Populations:** Patients with any grade of CRS treated with any dose of tocilizumab. This included 58 patients from the CTL019 trials, and 45 patients from the KTE-C19 trials.
- **Efficacy Populations:** Patients with grade 3-4 first episode of CRS treated with the recommended dose of tocilizumab. These included 45 patients from the CTL019 trials, and 15 patients from the KTE-C19 trials.

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Baseline Demographics and Other Characteristics

Table 11 shows the demographic characteristics of the Efficacy and Treated Populations derived from the patients with CRS in the series of CTL019 trials and KTE-C19 trials.

Table 11: Demographics

Demographic variable	CTL019 Series		KTE-C19 Series	
	Efficacy Population (n=45)	Treated Population (n=58)	Efficacy Population (n=15)	Treated Population (n=76)
Median age, years (range)	12.0 (3-23)	14.0 (3-75)	60.0 (9-75)	58.0 (4-76)
Age category, years - n (%)				
< 2	0	0	0	0
2 - <12	20 (44.5)	23 (39.7)	1 (6.7)	2 (2.6)
12 - <18	15 (33.3)	16 (27.6)	0	1 (1.3)
≥ 18	10 (22.2)	19 (32.7)	14 (93.3)	73 (96.1)
Sex - n (%)				
Male	24 (53.3)	35 (60.3)	10 (66.7)	53 (69.7)
Female	21 (46.7)	23 (39.7)	5 (33.3)	23 (30.3)
Race - n (%)				
White	37 (82.2)	50 (86.2)	13 (86.7)	67 (88.2)
Asian	1 (2.2)	1 (1.7)	0	0
Other	7 (15.6)	7 (12.1)	2 (13.3)	9 (11.8)
Ethnicity				
Hispanic or Latino	7 (15.6)	8 (13.8)	4 (26.7)	22 (28.9)
Other	38 (84.4)	50 (86.2)	11 (73.3)	54 (71.1)
Underlying malignancy				
ALL	45 (100)	52 (89.7)	2 (13.3)	17 (22.4)
CLL	0	6 (10.3)	0	0
DLBCL	0	0	12 (80.0)	35 (46.1)
MCL	0	0	0	13 (17.1)
TFL	0	0	0	9 (11.8)
PMBCL	0	0	1 (6.7)	2 (2.6)

Source: FDA analysis

Abbreviations: ALL, Acute lymphoblastic leukemia; CLL, Chronic lymphocytic leukemia; r/r, Relapsed or refractory; DLBCL, Diffuse large B cell lymphoma; MCL, Mantle cell lymphoma; TFL, Transformed follicular lymphoma; PMBCL, Primary mediastinal B cell lymphoma.

Review Comment: The Efficacy Populations are small and skewed for gender and race. Additionally, there are no children < 3 years old, and the primary cancer is limited to B-cell malignancies. Nonetheless, the efficacy outcomes can likely be extrapolated to a broader population on the basis of the pathogenesis of CRS and the mechanism of action of tocilizumab.

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Table 12 shows the CRS characteristics and tocilizumab treatments for the Efficacy and Treated Populations derived from the patients with CRS in the series of CTL019 trials and KTE-C19 trials.

Table 12: CRS Characteristics and Treatment

Characteristics n (%)	CTL019 Series		KTE-C19 Series	
	Efficacy Population (n=45)	Treated Population (n=58)	Efficacy Population (n=15)	Treated Population (n=76)
Baseline CRS Grade				
Grade 1	0 ^a	0	0	21 (27.6)
Grade 2	0	2 (3.5)	0	39 (51.3)
Grade 3	10 (22.2)	15 (25.8)	14 (93.3)	14 (18.4)
Grade 4	35 (77.8)	41 (70.7)	1 (6.7%)	1 (1.3)
Grade 5	0	0	0	0
Missing	0	0	0	1 (1.3)
CRS Duration prior to Tocilizumab				
0-4 Days	23 (51.1)	32 (55.2)	12 (80.0)	57 (75.0)
> 4 days	22 (48.9)	26 (44.8)	3 (20.0)	19 (25.0)
Number of Tocilizumab Doses				
1 dose	25 (55.5)	34 (58.6)	6 (40.0)	26 (34.2)
2 doses	13 (28.9)	17 (29.3)	5 (33.3)	23 (30.3)
≥ 3 doses	7 (15.6)	7 (12.1)	4 (26.7)	27 (35.5)
Number of Tocilizumab Doses Daily				
Single Tocilizumab Dose	43 (95.6)	56 (96.6)	10 (66.7)	64 (84.2)
BID or TID Dosing	2 (4.4)	2 (3.4)	5 (33.3)	12 (15.8)
First Tocilizumab Dose Level^b				
4 mg/kg	0	9 (15.5)	0	9 (11.8)
8 mg/kg	38 (84.4)	41 (70.7)	15 (100%)	67 (88.2)
12 mg/kg	7 (15.6)	8 (13.8)	0	0

Source: FDA analysis

^an (%)

^bCategorization from actual dose administered (0.1 - 5.2 mg/kg for the 4 mg/kg category, 6.1-9.8 mg/kg for the 8 mg/kg category, and 11.2 - 12.0 mg/kg for the 12 mg/kg category).

In the Efficacy Population from the CTL019 series, the median time from start of CRS to first dose of tocilizumab was 4 days (range, 0–18 days), nearly all patients were treated with one tocilizumab dose per day, and the median total number of tocilizumab doses was 1 (range, 1-4). In the Efficacy Population from the KTE-C19 series, the median time from start of CRS to first dose of tocilizumab was 3 days (range, 0-14 days), one third of the patients received 2 or 3 doses of tocilizumab per day, and the median total number of tocilizumab doses was 2 (range, 1-13).

Primary Endpoint

Response at day 14 was assessed as the primary efficacy endpoint for tocilizumab in the 45

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patients in the Efficacy Population for the CTL019 series and in the 15 patients in the Efficacy Population for the KTE-C19 series. Table 13 shows the results.

Table 13: Primary Endpoint Results in the Efficacy Populations

	CTL019 Series	KTE-C19 Series
	Efficacy Population (n=45)	Efficacy Population (n=15)
Day-14 Response (N)	31	8
% (95% CI),	68.9 (53.4, 81.8)	53.3 (30.1, 75.2)

Source: FDA analysis

Other Endpoints

For the 31 day-14 responders in the CTL019 series, the median time to response was 4 days (range, 1-12 days) after treatment with tocilizumab. For the 8 day-14 responders in the KTE-C19 series, the median time to response was 4.5 days (range, 2-7 days after treatment with tocilizumab).

The outcome of response was also assessed at 2, 7 and 21 days from the first dose of tocilizumab in the Efficacy Populations. Table 14 shows the response rates at each of these additional timepoints.

Table 14: Additional Endpoint Results in the Efficacy Populations

	CTL019 Series (n=45)		KTE-C19 Series (n=15)	
	Responders	% (95% CI)	Responders	% (95% CI)
Response by Day 2	9	20.0 (9.6, 34.6)	3	20.0 (4.3, 48.1)
Response by Day 7	26	57.8 (42.2, 72.3)	8	53.3 (26.6, 78.7)
Response by Day 14 (Primary)	31	68.9 (53.4, 81.8)	8	53.3 (26.6, 78.7)
Response by Day 21	31	68.9 (53.4, 81.8)	8	53.3 (26.6, 78.7)

Source: FDA analysis

Review Comment: In both series, the majority of the patients who achieved the response criteria did so within 7 days of the first dose of tocilizumab, but there were 5 additional responders after 7 days in the CTL019 series. It is not clear whether these additional responses were due to tocilizumab or to the natural resolution of CRS with supportive care.

Subpopulations

Table 15 summarizes subgroup analyses for the 45 day-14 responders in the Efficacy Population for the CTL019 series and in the 15 patients in the Efficacy Population for the KTE-C19 series.

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There was no outlier in the subgroups of age, sex, race, ethnicity, grade of CRS as first dose of tocilizumab, or duration of CRS prior to treatment with tocilizumab. However, the numbers of patients are small in all subgroups.

Table 15: Subgroup Analyses of Day-14 Response in the Efficacy Populations

	CTL019 Series		KTE-C19 Series	
	Responders/N	% (95% CI)	Responders/N	% (95% CI)
Age groups, years				
2 - <12	12/20	60.0 (36.1, 80.9)	1/1	100.0 (2.5, 100.0)
12 - <18	13/15	86.7 (59.5, 98.3)	0/1	0 (0.0, 95.0)
≥ 18	6/10	60.0 (26.2, 87.8)	7/14	50.0 (23.0, 77.0)
Sex				
Male	17/24	70.8 (48.9, 87.4)	6/10	60.0 (26.2, 87.8)
Female	14/21	66.7 (43.0, 85.4)	2/5	40.0 (5.3, 85.3)
Race				
White	26/37	70.3 (53.0, 84.1)	7/13	53.8 (25.1, 80.8)
Asian	1/1	100.0 (2.5, 100.0)	0/0	N/A
Others	4/7	57.1 (18.4, 90.1)	1/2	50.0 (1.3, 98.7)
Ethnic				
Hispanic or Latino	4/7	57.1 (18.4, 90.1)	3/4	75.0 (19.4, 99.4)
Others	27/38	71.1 (54.1, 84.6)	5/11	45.5 (16.7, 76.6)
Baseline CRS Grade				
Baseline Grade 3	8/10	80.0 (44.4, 97.5)	8/14	57.1 (28.9, 82.3)
Baseline Grade 4	23/35	65.7 (47.8, 80.9)	0/1	0 (0.0, 95.0)
CRS Prior Duration				
0-4 days before tocilizumab	14/23	60.9 (38.5, 80.3)	5/12	41.7 (15.2, 72.3)
> 4 days before tocilizumab	17/22	77.3 (54.6, 92.2)	3/3	100.0 (29.2, 100.0)

Source: FDA analysis

Review Comment: The day-14 response results across the demographic and baseline characteristics subgroups are similar to those in the primary analysis.

Additional Efficacy Considerations

Intended Population Considerations

The sponsor proposed to indicate tocilizumab for treatment of patients with severe or life-threatening CRS. As shown in Table 12 above, 79% of the patients in the Treated Population from the KTE-C19 series had only mild (Grade 1) or moderate (Grade 2) CRS when first treated with tocilizumab. The day-14 response was 57.1% (95% CI 34.0, 78.2) for patients with mild CRS and 56.4% (95% CI 39.6, 72.2) for patients with moderate CRS.

To determine how well early treatment with tocilizumab prevented worsening of CRS, a shift analysis was performed. Table 16 shows the shift in CRS grade at baseline to the worst grade

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after treatment with tocilizumab in the Treated Population from the CTL019 and KTE-C19 series.

Table 16: Shift Table for CRS Grade in the Treated Population

	CTL019 Series				KTE-C19 Series			
	Treated Population (n=58)				Treated Population (n=76)			
	<u>Maximal CRS Grade</u>				<u>Maximal CRS Grade</u>			
	2	3	4	5	2	3	4	5
CTL019-CRS								
Baseline CRS Grade 2 (n= 2)	2	0	0	0				
Baseline CRS Grade 3 (n= 15)	0	13	2	0				
Baseline CRS Grade 4 (n= 41)	0	0	41 ^a	0				
KTE-C19-CRS								
Baseline CRS Grade 1 (n=21)					13	7	1	0
Baseline CRS Grade 2 (n= 39)					31	5	2	1
Baseline CRS Grade 3 (n= 14)					0	12	1 ^a	1
Baseline CRS Grade 4 (n= 1)					0	0	1	0

Source: FDA analysis using sponsor's grading

^aThree patients in the CTL019 series (CCTL019B2202_1401009, CCTL019B2205J_1003005, CCTL019B2205J_1003008) and one in the KTE-C19 series (101-003-025) died with active CRS although the cause of death was listed as the primary malignancy.

Review Comment: Although the day-14 response rates for the patients in the Treated Populations from the KTE-019 series with mild or moderate CRS were similar to those for patients with severe CRS, it is not clear that there is a need for tocilizumab with such mild CRS. The shift analysis shows that few patients with Grade 3 or 4 CRS progress to a higher grade after treatment with tocilizumab, but in the KTE-C19 series there were multiple patients treated with mild or moderate CRS who progressed to a worse grade. This suggests that tocilizumab was not effective when used for the treatment of mild disease. This is consistent with the mechanisms of action in that tocilizumab does not prevent activation of T cells and may not be useful if used as prophylaxis or pre-emptively. Hence, the data support including only the patients with severe or life-threatening CRS in the intended population.

Dosing Considerations

There was no dose-ranging study to determine the minimal individual dose, the optimal schedule, or the maximal number of doses for treatment of CRS. The most common doses of tocilizumab used for treatment of CAR T cell-induced CRS are those currently approved for use in SJIA and other indications, and the sponsor proposes the same doses for the CRS indication.

The patients with CRS from the CTL019 series and the KTE-C19 series were treated with a variety of doses and dosing regimens. For the derivation of the Efficacy Population, only those

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patients treated with the recommended doses (see Table 11) were included in the primary endpoint analysis. Table 17 shows the day-14 responses by number of tocilizumab doses administered, the tocilizumab regimen used, and the categorization for the first dose of tocilizumab administered in the Efficacy Populations.

Table 17: Day-14 Response by Dosing in the Efficacy Populations

	CTL019 Series		KTE-C19 Series	
	Responders/N	% (95% CI)	Responders/N	% (95% CI)
Number of Tocilizumab Doses				
1	24/25	96.0 (79.6, 99.9)	5/6	83.3 (35.9, 99.6)
2	7 / 13	53.8 (25.1, 80.8)	3/5	60.0 (14.7, 94.7)
Tocilizumab Regimen				
Single Dose	31/43	72.1 (56.3, 84.7)	4/10	40.0 (12.2, 73.8)
BID or TID Dosing	0/2	0 (0.0, 77.6)	4/5	80.0 (28.4, 99.5)
First Tocilizumab Dose Level				
8 mg/kg	27/38	71.1 (54.1, 84.6)	8/15	53.3 (26.6, 78.7)
12 mg/kg	4/7	57.1 (18.4, 90.1)	0/0	N/A

Source: FDA analysis

Table 18 shows day-14 responses by number of tocilizumab doses administered, the tocilizumab regimen used, and the categorization for the first dose of tocilizumab administered in the Treated Populations. It was noted that day-14 responses were observed even with the 4 mg/kg dose of tocilizumab.

Table 18: Day-14 Response by Dosing in the Treated Populations

	CTL019 Series		KTE-C19 Series	
	Responders/N	% (95% CI)	Responders/N	% (95% CI)
All Treated Population				
	43/58	74.1 (61.0, 84.7)	42/76	55.3 (43.4, 66.7)
Number of Tocilizumab Doses				
1	33/34	97.1 (84.7, 99.9)	23/26	88.5 (69.8, 97.6)
2	10/17	58.8 (32.9, 81.6)	19/23	82.6 (61.2, 95.0)
Tocilizumab Regimen				
Single TCZ Dose	43/56	76.8 (63.6, 87.0)	35/64	54.7 (41.7, 67.2)
BID or TID Dosing	0/2	0 (0.0, 77.6)	7/12	58.3 (27.7, 84.8)
First Tocilizumab Dose				
4 mg/kg	8/9	88.9 (51.8, 99.7)	5/9	55.6 (21.2, 86.3)
8 mg/kg	30/41	73.2 (57.1, 85.8)	37/67	55.2 (42.6, 67.4)
12 mg/kg	5/8	62.5 (24.5, 91.5)	0/0	N/A

Source: FDA analysis

The responders by definition were limited to patients receiving no more than 2 doses of tocilizumab. In the Treated Population there were additional patients who became afebrile and off vasopressors within 14 days using more than 2 doses of tocilizumab. In the CTL-019 series,

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these included 4 of 7 patients treated with 3 or 4 doses; in the KTE-C19 series, this included 10 of 12 patients treated with 3 or 4 doses and 11 of 15 patients treated with 5 or more doses.

Review Comment: The conclusions that can be drawn from the analyses by dosing are few.

- Many patients have rapid resolution of CRS with only 1 or 2 doses of tocilizumab (Tables 17 and 18). When patients have resolution of CRS after more than 2 doses, it is not clear how much the additional doses contributed. However, since the protocols instructed use of tocilizumab only in patients with persisting severe or life-threatening CRS, it would be warranted to allow the maximum safe number of doses in practice in the absence of data that identify when further treatment would be futile.*
- It was notable that some patients in the Treated Population had resolution of CRS by day 14 after receiving tocilizumab 4 mg/kg, suggesting that a dose lower than recommended might be effective. However, it is possible that the lower dose was chosen for patients who were clinically less symptomatic. Additionally, the number of patients is small. Consequently, more data would be needed to support the lower dose.*
- The day-14 response rate appeared to be higher in patients who received multiple doses per day in the Efficacy Population but not in the Treated Population. However, the number of patients who received multiple doses per day is small, so in the face of the inconsistent results, the data do not support requiring multiple doses per day over once daily dosing.*
- Overall, the data do not resolve many of the uncertainties about the optimal dose and schedule of tocilizumab for treatment of CAR T cell-induced CRS.*

Literature Review

The first report of tocilizumab being used successfully to treat CAR T cell-induced CRS involved a 7-year-old female patient with ALL (Grupp, Kalos et al. 2013). The first case of blinatumomab-induced CRS treated with tocilizumab was a 7-year-old male patient with B-ALL (Teachey, Rheingold et al. 2013). Treatment with a dose of tocilizumab (8 mg/kg IV) resulted in a clinical improvement of CRS. Additionally, (Davila, Riviere et al. 2014) reported that tocilizumab was as effective as steroids for CAR T cell-induced CRS, but that it did not eradicate the CAR T cells as steroid did.

The first and only series describing the use of tocilizumab treatment for CAR T cell-induced CRS was published by (Fitzgerald, Weiss et al. 2017). In this retrospective review, 18 of 39 patients (46%) developed grade 3-4 CRS, 14 of whom required treatment with vasopressors and 6 of whom required mechanical ventilation. Thirteen subjects were treated with tocilizumab (dose not stated). The authors report that “Nine subjects received one dose, and four subjects received two or three doses of tocilizumab due to partial response or recurrence of symptoms after initial dose. The first dose of tocilizumab was administered a median of 5 days after CTL019 infusion. Fever and tachycardia improved rapidly after tocilizumab administration. Subjects defervesced a median of 4 hours (IQR, 2–5) after tocilizumab administration. Concomitant with this, their overall clinical appearance markedly improved within hours of

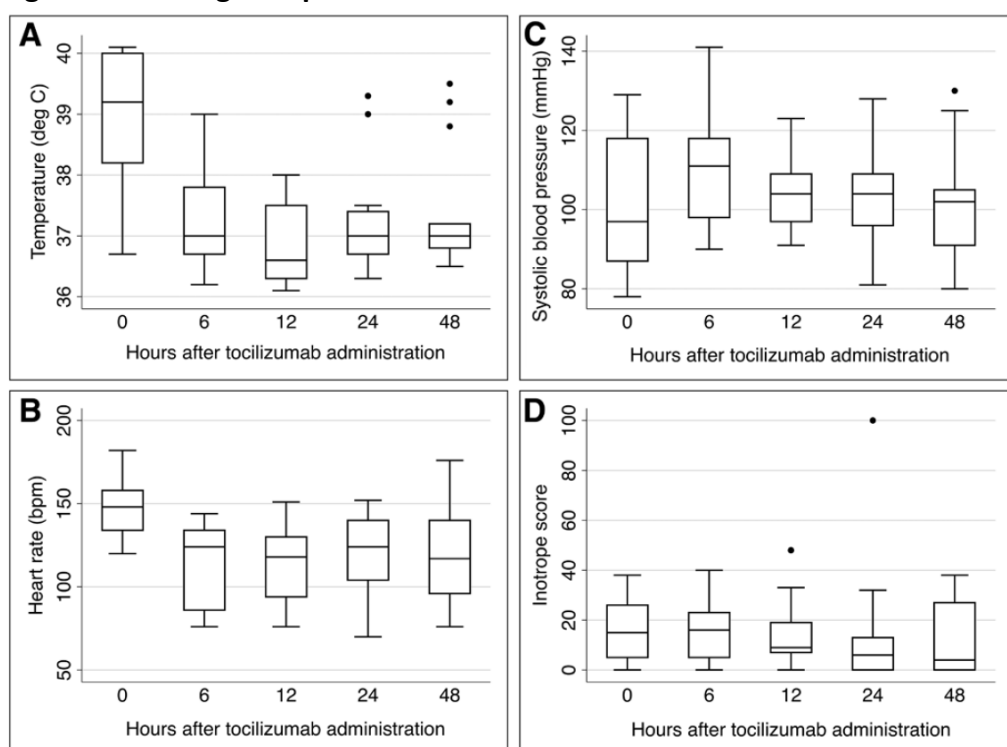
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tocilizumab administration. Nevertheless, catecholamine-dependent shock resolved over days rather than hours, with complete resolution a median of 4 days (IQR, 2–4) after tocilizumab administration. Eight subjects were also treated with short courses of corticosteroids (median, 6.5 d) for refractory hypotension: five received hydrocortisone, two received methylprednisolone, and one received both. All four subjects treated with multiple doses of tocilizumab also received corticosteroids. All patients requiring tocilizumab and/or steroids for grade 4 CRS subsequently achieved disease remission and survived CRS.” Figure 2 shows changes in temperature, heart rate, systolic blood pressure and inotrope score for the first 48 hours after administration of tocilizumab.

Figure 2: Vital Sign Response After Tocilizumab for CAR T Cell-Induced CRS



Source: Fitzgerald, Weiss et al. 2017, Figure 3

Methodology for identifying literature:

The Sponsor and FDA clinical review team conducted a comprehensive literature search using PubMed to identify publications on the use of tocilizumab for the treatment of drug-induced CRS using the following strategy:

- “tocilizumab” and “cytokine release syndrome”;
- “tocilizumab” and “cytokine storm”;
- “tocilizumab” and “chimeric antigen receptor therapy”;
- “tocilizumab” and “CTL019”;
- “tocilizumab” and “KTE-C19”;

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“tocilizumab” and “blinatumomab”;
“cytokine release syndrome” and “chimeric antigen receptor therapy”;
“cytokine release syndrome” and “CTL019”;
“cytokine release syndrome” and “KTE-C19”;
“cytokine release syndrome” and “blinatumomab”;
“cytokine release syndrome”;
“cytokine storm”.

Those publications with tocilizumab used as a treatment for CRS were included in the final tabulation. In addition, the Sponsor searched the ClinicalTrials.gov and NIH GeMCRIS database for clinical trials investigating tocilizumab for the treatment of CRS. The 55 cases of use of tocilizumab for treatment of CRS following immunotherapy that were identified are listed in Table 19.

Table 19: Literature Reviewed - Tocilizumab Treatment of CRS

Publication	Immunotherapy	Patients	No. of Patients Treated with TOCILIZUMAB (TOCILIZUMAB Dosing Regimen)	Reported CRS Outcome after TOCILIZUMAB
(Grupp, Kalos et al. 2013) (Manuscript)	CTL019 (2 nd generation CD19 CAR [CD137/CD3])	Pediatric ALL	1 patient TOCILIZUMAB+ETN+CS (TOCILIZUMAB 8 mg/kg)	1/1 resolved ^a
(Teachey, Rheingold et al. 2013) (Manuscript)	Blinatumomab (BiTE)	Pediatric ALL	1 patient TOCILIZUMAB+CS (TOCILIZUMAB 8 mg/kg)	1/1 resolved
(Maude, Frey et al. 2014) (Manuscript)	CTL019	Pediatric and young adult ALL	9 patients TOCILIZUMAB only, 3 patients; TOCILIZUMAB+CS, 6 patients 4 patients received TOCILIZUMAB 2 (TOCILIZUMAB dose not reported)	9/9 resolved ^a
(Grupp, Maude et al. 2014) (Abstract)	CTL019	Pediatric and young adult ALL	11 patients TOCILIZUMAB only, 6 patients; TOCILIZUMAB+CS, 5 patients (TOCILIZUMAB dose/no. of doses not reported)	11/11 resolved ^a
(Grupp, Maude et al. 2015) (Abstract)	CTL019	Pediatric and young adult ALL	15 patients TOCILIZUMAB only, 6 patients, TOCILIZUMAB+CS, 9 patients (TOCILIZUMAB dose/no. of doses not reported)	15/15 resolved ^a
(Frey, Levine et al. 2014) (Abstract)	CTL019	Adult ALL	9 patients Details provided for 3 refractory patients only:	6/9 resolved 3/9 died ^b

Table 19: Literature Reviewed - Tocilizumab Treatment of CRS

Publication	Immunotherapy	Patients	No. of Patients Treated with TOCILIZUMAB (TOCILIZUMAB Dosing Regimen)	Reported CRS Outcome after TOCILIZUMAB
			TOCILIZUMAB+CS, 1 patient (TOCILIZUMAB 4 mg/kg x2); TOCILIZUMAB+ETN+CS, 1 patient (TOCILIZUMAB 8 mg/kg x3); TOCILIZUMAB+STX+CS, 1 patient (TOCILIZUMAB 8 mg/kg x2, STX x2)	
(Porter, Lacey et al. 2014) (Abstract)	CTL019	Adult CLL	7 patients TOCILIZUMAB +/- CS, 7 patients; several patients also received CS and/or ETN (TOCILIZUMAB dose/no. of doses not reported)	7/7 resolved ^c
(Porter, Frey et al. 2017) (Abstract)	CTL019	Adult CLL	3 patients TOCILIZUMAB +/-CS +/- anti-cytokine therapy (TOCILIZUMAB dose/no. of doses not reported)	3/3 resolved ^c
(Porter, Hwang et al. 2015) (Manuscript)	CTL019	Adult CLL	4 patients TOCILIZUMAB only, 2 patients; TOCILIZUMAB+CS, 2 patients (TOCILIZUMAB dose/no. of doses not reported)	4/4 resolved ^c
(Lee, Stetler-Stevens et al. 2014) (Abstract)	2 nd generation CD19 CAR [CD28/CD3]	ALL, NHL	4 patients TOCILIZUMAB alone, 2 patients; TOCILIZUMAB+CS (TOCILIZUMAB dose/no. of doses not reported)	4/4 resolved ^d
(Lee, Kochenderfer et al. 2015) (Manuscript)	2 nd generation CD19 CAR [CD28/CD3]	Pediatric and young adult ALL, NHL	4 patients TOCILIZUMAB alone, 2 patients; TOCILIZUMAB+CS, 2 patients (TOCILIZUMAB dose/no. of doses not reported)	4/4 resolved ^d
(Davila, Riviere et al. 2014) (Manuscript)	2 nd generation CD19 CAR [CD28/CD3]	Adult B-ALL	4 patients TOCILIZUMAB alonex1, 1 patient; TOCILIZUMAB alonex2, 2 patients; TOCILIZUMAB+CSx1, 1 patient (TOCILIZUMAB dose not reported)	4/4 resolved ^e
(Park, Riviere et al. 2014) (Abstract)	2 nd generation CD19 CAR [CD28/CD3]	Adult B-ALL	9 patients IL-6R antagonist or CS (TOCILIZUMAB dose/no. of doses not reported)	9/9 resolved ^{e,f}

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Table 19: Literature Reviewed - Tocilizumab Treatment of CRS

Publication	Immunotherapy	Patients	No. of Patients Treated with TOCILIZUMAB (TOCILIZUMAB Dosing Regimen)	Reported CRS Outcome after TOCILIZUMAB
(Curran, Riviere et al. 2014) (Abstract)	2 nd Generation CD19 CAR [CD28/CD3]	Pediatric and young adult B-ALL	2 patients TOCILIZUMAB or CS (TOCILIZUMAB dose/no. of doses not reported)	2/2 resolved ^g
(Curran, Riviere et al. 2015) (Abstract)	2 nd Generation CD19 CAR [CD28/CD3]	Pediatric and young adult B-ALL	5 patients TOCILIZUMAB or CS (TOCILIZUMAB dose/no. of doses Not reported)	5/5 resolved ^g
(Sauter, Riviere et al. 2014) (Abstract)	2nd Generation CD19 CAR [CD28/CD3] after SCT	Adult B-NHL	2 patients TOCILIZUMAB only 4 mg/kg [11], TOCILIZUMAB+CS, 1 patient (TOCILIZUMAB dose/no. of doses not reported)	2/2 resolved
(Schuster, Svoboda et al. 2014) (Abstract)	CTL019	Adult NHL	1 patient TOCILIZUMAB+CS (TOCILIZUMAB dose/no. of doses not reported)	1/1 resolved ^h
(Kochenderfer, Dudley et al. 2015) (Manuscript)	2nd generation CD19 CAR [CD28/CD3]	Adult DLBCL or indolent B-cell malignancy	2 patients TOCILIZUMAB only (TOCILIZUMAB dose/no. of doses not reported)	2/2 did not improve i
(Brudno and Kochenderfer 2016) (Manuscript))	CD269 CAR CD19 CAR	Adult ALL	2 patients TOCILIZUMAB x2, 1 patient TOCILIZUMAB x1, 1 patient (TOCILIZUMAB dose not provided)	2/2 improved
(Lee, Stetler-Stevenson et al. 2015) (Abstract)	2nd generation CD19 CAR [CD28/CD3]	Pediatric and young adult ALL	1 patient TOCILIZUMAB+CS (TOCILIZUMAB dose/no. of doses not reported)	1/1 resolved
(Locke, Neelapu et al. 2015) (Abstract)	KTE-C19 (2nd generation CD19 CAR [CD28/CD3])	Adult NHL	1 patient TOCILIZUMAB+CS (TOCILIZUMAB dose/no. of doses not reported)	Not provided but assumed resolved ^j
(Dong, Chang et al. 2015) (Abstract)	4SCAR19 (4th generation CD19 CAR [CD28/CD137/CD27/CD3])	Adult and pediatric ALL	11 patients ETN or TOCILIZUMAB, 8 patients ETN+TOCILIZUMAB, 3 patients (ETN 12.5 mg, TOCILIZUMAB 8 mg/kg, no. of doses not reported)	Not provided, but assumed resolved
(Luo, Chang et al. 2015) (Abstract)	4SCAR123 (4th generation	Adult AML	1 patient TOCILIZUMAB only	1/1 resolved

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Table 19: Literature Reviewed - Tocilizumab Treatment of CRS

Publication	Immunotherapy	Patients	No. of Patients Treated with TOCILIZUMAB (TOCILIZUMAB Dosing Regimen)	Reported CRS Outcome after TOCILIZUMAB
	CD123 CAR [CD28/CD137/CD27/CD3])		(TOCILIZUMAB dose/no. of doses not reported)	
22 Publications (total from literature search in June 2016):	Publications: 19 for 2nd gen CD19 CAR; 1 for 4th gen CD19 CAR; 1 for 4th gen CD123 CAR; 1 CD19 bispecific antibody 1 CD19 and CD269 CAR (gen not reported)	Population: Pediatric or adult ALL, and adult CLL, NHL (DLBCL), or AML	Treated with TOCILIZUMAB: ≥ 55 patients Where provided: TOCILIZUMAB x1, 10 patients; TOCILIZUMAB x 2, 9 patients; TOCILIZUMAB x 3, 1 patient Where provided: 8 mg/kg, 12 patients; 4 mg/kg, 2 patients	CRS Resolved: ≥ 50 patients
(Grupp, Laetsch et al. 2016) (Abstract); phase II ELIANA study	CTL019	Adult and pediatric ALL	25 patients	Complete resolution of all CRS events
(Locke, Neelapu et al. 2017) (Abstract); phase II ZUMA-1 study	KTE-C19	Adult NHL	43 patients TOCILIZUMAB 27 patients steroids	CRS reversible except for 1 case of HLH and 1 case of cardiac arrest
(Tanyi, Stashwick et al. 2017), (Manuscript)	Mesothelin-targeted CAR-T Cells	Adult ovarian cancer	1 patient	1/1 resolved
(Rotz, Leino et al. 2017), (Manuscript)	Anti-PD-1 antibody nivolumab	Adult sarcoma	1 patient TOCILIZUMAB+CS (TOCILIZUMAB 4 mg/kg x1) (TOCILIZUMAB 8 mg/kg x1)	1/1 resolved

Source: BLA 125276 eCTD Module 2 and PubMed

Notes: ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CS: corticosteroids; DLBCL: diffuse large B-cell lymphoma; ETN: etanercept; NHL: non-Hodgkin's lymphoma; SCT: stem cell transplant; STX: siltuximab; TOCILIZUMAB: tocilizumab.

a Counted as a total of 15 patients treated with TOCILIZUMAB.

b All 3 patients had significant disease burden at baseline and had significant infectious complications.

c Counted as a total of 7 patients treated with TOCILIZUMAB.

d Counted as a total of 4 patients treated with TOCILIZUMAB.

e Counted as a total of 4 patients treated with TOCILIZUMAB (i.e., at least 4 patients).

f Assumed resolved for all 9 patients but not specifically stated (previous publication reported resolved for 4 patients).

g Counted as a total of 1 patient treated with TOCILIZUMAB (i.e., at least 1 patient).

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Table 19: Literature Reviewed - Tocilizumab Treatment of CRS

Publication	Immunotherapy	Patients	No. of Patients Treated with TOCILIZUMAB (TOCILIZUMAB Dosing Regimen)	Reported CRS Outcome after TOCILIZUMAB
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h Assumed resolved as there was no treatment-related mortality but was not specifically stated.

i TOCILIZUMAB used in 2 patients with Grade 3 and 4 toxicity. One had hypotension, and the other had predominantly neurologic toxicity. The toxicity did not substantially improve in either patient.

j TOCILIZUMAB used in 1 patient with Grade 4 encephalopathy and CRS. Assumed resolved, as the patient subsequently died within 30 days of

KTE-C19 cell infusion due to an intracranial hemorrhage deemed unrelated to KTE-C19 per the investigator.

k Assumed resolved as the median follow-up was 4 months (range: 3-24 months).

l Counted as a total of 4 patients treated with TOCILIZUMAB (i.e., at least 4 patients).

m The Sponsor does not have access to patient level data from these trials, but has sought letters of authorization from the study sponsors granting FDA permission to review the data on the use of TOCILIZUMAB to treat CRS. As the Agency will be conducting its own analysis of the data from these studies, the information summarized in the table based on meeting abstracts are presented separately, and have not been added to the total counts based on the literature search.

The dose of tocilizumab administered (when stated) was either 4 or 8 mg/kg IV. Across the studies, tocilizumab was administered as either a single dose or two doses (where stated), with repeat-dose administration given occasionally (Frey, Levine et al. 2014). In a recent review, tocilizumab dosing ranges were reported from 4 to 8 mg/kg (maximum of 800 mg/dose) by intravenous (IV) infusion over 60 minutes were reported as common (Shank, Do et al. 2017).

For the vast majority of these patients, treatment with tocilizumab was successful in rapidly resolving the signs and symptoms of CRS. A negative impact on the anti-leukemic properties of the cancer immunotherapy was not reported (Davila, Riviere et al. 2014) (Maude, Frey et al. 2014) (Porter, Hwang et al. 2015).

There were reported cases of CRS which were refractory to tocilizumab therapy. The refractory cases all occurred in adult ALL patients with significant disease burden who received CAR T-cells (Frey, Levine et al. 2014) (Kochenderfer, Dudley et al. 2015) .

Review Comment: There are numerous reports in the published literature with results consistent with an effect of tocilizumab on severe or life-threatening CRS. The data provided by (Fitzgerald, Weiss et al. 2017) showing rapid normalization of vital signs is compelling objective evidence of the activity of tocilizumab.

7.3.2 Integrated Assessment of Effectiveness

The efficacy of ACTEMRA for the treatment of CRS was assessed in a retrospective analyses of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies. Evaluable patients had been treated with tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the

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first episode of CRS was included in the analysis. Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, no more than 2 doses of tocilizumab were needed, and no drugs other than tocilizumab and corticosteroids were used for treatment. Thirty-one patients (69%; 95% CI: 53%-82%) achieved a response. Achievement of resolution of CRS within 14 days was confirmed in a second study using an independent cohort that included 15 patients (range: 9-75 years old) with CAR T cell-induced CRS. The literature review supported the conclusion that tocilizumab has activity in the treatment of CRS.

7.4. Review of Safety

7.4.1. Safety Review Approach

See Section 7.1 for the description of the sources of data used for the safety review and the approach to pooling. In addition to the cross-referenced information in BLA 125643 and BLA 125646, the safety review also relied on prior findings from studies of tocilizumab in healthy volunteers and in patients with SJIA in BLA 125276.

7.4.2. Review of the Safety Database

The populations used in the safety review are shown in Table 10 above. In CTL-019 BLA studies, there were 58 patients who received at least one dose of tocilizumab. The median age was 14 years (range: 3 to 75 years). In KTE-C19 BLA, there were 83 patients who received at least one dose of tocilizumab, the median age was 58 years (range: 4 to 75 years). Of these 83 patients who received 1 or more doses of tocilizumab, only 76 patients received tocilizumab for CRS treatment, while 7 patients received tocilizumab for CRS prophylaxis. The demographics of the patients in the safety database are described in Table 11.

Review Comment: The size of the safety database is relatively small, but since the CAR T cell-induced CRS population is quite limited, the small size could be acceptable with high-quality data and supporting findings in related intended populations. There is not sufficient information to evaluate for any dose-toxicity relationships.

7.4.3. Adequacy of Sponsor's Clinical Safety Assessments

There were no specific assessments for safety of tocilizumab in the clinical trials of CTL019 or KTE-C19. For the CTL019 trials, information was passively reported. For the KTE-C19 trials, limited aggregation of treatment-emergent adverse events was provided. The studies did not require investigators to determine the causality of adverse events with respect to specifically tocilizumab. Therefore such information is not available.

Review Comment: The data provided specifically regarding safety of tocilizumab in patients with CAR T cell-induced CRS are clearly incomplete.

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7.4.4. Safety Results

Deaths

Five patients in the CTL019 series and six patients in the KTE-C19 series died within 30 days of the first dose of tocilizumab. None of the deaths were attributed to tocilizumab.

Treatment Emergent Adverse Events and Adverse Reactions

For the clinical trials of CTL-019, there were no reports of adverse events attributable to tocilizumab (BLA 125646 Response to Information Request dated 6/28/2017 Section 2.8).

For the clinical trials of KTE-C19, available safety data were limited to infections, neutropenia, anemia, thrombocytopenia, gastrointestinal perforation, and liver toxicity for those with or without use of tocilizumab for patients with CRS in ZUMA-1, ZUMA-2, ZUMA-3 and ZUMA-4 combined (Table 20).

Table 20: KTE-C19 - Selected Adverse Events

	Did Not Receive Tocilizumab (N=64)		Received Tocilizumab (N=83)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bacterial Infections				
Bacterial sepsis	0 (0)	0 (0)	1 (1)	1 (1)
Cellulitis	0 (0)	0 (0)	1 (1)	1 (1)
Clostridium difficile colitis	2 (3)	1 (2)	2 (2)	2 (2)
Clostridium difficile infection	1 (2)	0 (0)	4 (5)	1 (1)
Enterobacter bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Enterococcal bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Escherichia bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Klebsiella infection	0 (0)	0 (0)	1 (1)	1 (1)
Pneumonia klebsiella	1 (2)	1 (2)	0 (0)	0 (0)
Pseudomonal bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Staphylococcal bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Viral Infections				
Cytomegalovirus infection	0 (0)	0 (0)	1 (1)	0 (0)
Cytomegalovirus viremia	1 (2)	0 (0)	0 (0)	0 (0)
Herpes simplex	0 (0)	0 (0)	1 (1)	0 (0)
Human herpesvirus 6 infection	0 (0)	0 (0)	1 (1)	1 (1)
Oral herpes	0 (0)	0 (0)	2 (2)	1 (1)
Parvovirus infection	0 (0)	0 (0)	1 (1)	1 (1)
Respiratory tract infection viral	1 (2)	0 (0)	0 (0)	0 (0)
Rhinovirus infection	0 (0)	0 (0)	1 (1)	0 (0)

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Table 20: KTE-C19 - Selected Adverse Events

	Did Not Receive Tocilizumab (N=64)		Received Tocilizumab (N=83)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3
Opportunistic Infections				
Bronchopulmonary aspergillosis	1 (2)	0 (0)	0 (0)	0 (0)
Candida infection	1 (2)	0 (0)	1 (1)	0 (0)
Fungal retinitis	0 (0)	0 (0)	1 (1)	1 (1)
Fungal skin infection	0 (0)	0 (0)	1 (1)	0 (0)
Mucormycosis	0 (0)	0 (0)	1 (1)	1 (1)
Oral candidiasis	0 (0)	0 (0)	3 (4)	0 (0)
Systemic candida	0 (0)	0 (0)	1 (1)	1 (1)
Tongue fungal infection	0 (0)	0 (0)	1 (1)	0 (0)
Other Pathogen Infections				
Bacteremia	1 (2)	0 (0)	0 (0)	0 (0)
Bronchitis	1 (2)	0 (0)	0 (0)	0 (0)
Conjunctivitis	0 (0)	0 (0)	1 (1)	0 (0)
Device related infection	1 (2)	1 (2)	0 (0)	0 (0)
Lung infection	0 (0)	0 (0)	1 (1)	1 (1)
Orbital infection	1 (2)	0 (0)	0 (0)	0 (0)
Pneumonia	1 (2)	0 (0)	2 (2)	2 (2)
Sepsis	0 (0)	0 (0)	1 (1)	1 (1)
Sinusitis	0 (0)	0 (0)	1 (1)	0 (0)
Urinary tract infection	1 (2)	0 (0)	6 (7)	5 (6)
GI perforation				
Esophageal fistula	0 (0)	0 (0)	1 (1)	1 (1)
Neutropenia				
Febrile neutropenia	18 (28)	17 (27)	22 (27)	20 (24)
Neutropenia	19 (30)	17 (27)	23 (28)	21 (25)
Neutrophil count decreased	23 (36)	23 (36)	17 (20)	15 (18)
Anemia				
Anemia	40 (63)	26 (41)	43 (52)	32 (39)
Thrombocytopenia				
Platelet count decreased	22 (34)	11 (17)	22 (27)	20 (24)
Thrombocytopenia	14 (22)	10 (16)	23 (28)	17 (20)
Liver Function				
Alanine aminotransferase increased	12 (19)	5 (8)	19 (23)	2 (2)
Ascites	1 (2)	0 (0)	2 (2)	1 (1)

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Table 20: KTE-C19 - Selected Adverse Events

	Did Not Receive Tocilizumab (N=64)		Received Tocilizumab (N=83)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Aspartate aminotransferase increased	13 (20)	4 (6)	17 (20)	3 (4)
Blood bilirubin increased	0 (0)	0 (0)	10 (12)	5 (6)
Hepatic enzyme increased	0 (0)	0 (0)	1 (1)	0 (0)
Hyperbilirubinemia	0 (0)	0 (0)	3 (4)	2 (2)
Liver function test increased	0 (0)	0 (0)	1 (1)	1 (1)
Transaminases increased	0 (0)	0 (0)	2 (2)	1 (1)
Infections and infestations				
Bacteremia	1 (2)	0 (0)	0 (0)	0 (0)
Bacterial sepsis	0 (0)	0 (0)	1 (1)	1 (1)
Bronchitis	1 (2)	0 (0)	0 (0)	0 (0)
Bronchopulmonary aspergillosis	1 (2)	0 (0)	0 (0)	0 (0)
Candida infection	1 (2)	0 (0)	1 (1)	0 (0)
Cellulitis	0 (0)	0 (0)	1 (1)	1 (1)
Clostridium difficile colitis	2 (3)	1 (2)	2 (2)	2 (2)
Clostridium difficile infection	1 (2)	0 (0)	4 (5)	1 (1)
Conjunctivitis	0 (0)	0 (0)	1 (1)	0 (0)
Cytomegalovirus infection	0 (0)	0 (0)	1 (1)	0 (0)
Cytomegalovirus viremia	1 (2)	0 (0)	0 (0)	0 (0)
Device related infection	1 (2)	1 (2)	0 (0)	0 (0)
Enterobacter bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Enterococcal bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Escherichia bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Fungal retinitis	0 (0)	0 (0)	1 (1)	1 (1)
Fungal skin infection	0 (0)	0 (0)	1 (1)	0 (0)
Herpes simplex	0 (0)	0 (0)	1 (1)	0 (0)
Human herpesvirus 6 infection	0 (0)	0 (0)	1 (1)	1 (1)
Klebsiella infection	0 (0)	0 (0)	1 (1)	1 (1)
Lung infection	0 (0)	0 (0)	1 (1)	1 (1)
Mucormycosis	0 (0)	0 (0)	1 (1)	1 (1)
Oral candidiasis	0 (0)	0 (0)	3 (4)	0 (0)
Oral herpes	0 (0)	0 (0)	2 (2)	1 (1)
Orbital infection	1 (2)	0 (0)	0 (0)	0 (0)
Parvovirus infection	0 (0)	0 (0)	1 (1)	1 (1)
Pneumonia	1 (2)	0 (0)	2 (2)	2 (2)
Pneumonia klebsiella	1 (2)	1 (2)	0 (0)	0 (0)
Pseudomonal bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Respiratory tract infection viral	1 (2)	0 (0)	0 (0)	0 (0)
Rhinovirus infection	0 (0)	0 (0)	1 (1)	0 (0)
Sepsis	0 (0)	0 (0)	1 (1)	1 (1)
Sinusitis	0 (0)	0 (0)	1 (1)	0 (0)

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Table 20: KTE-C19 - Selected Adverse Events

	Did Not Receive Tocilizumab (N=64)		Received Tocilizumab (N=83)	
	Any Grade	Grade $\geq$ 3	Any Grade	Grade $\geq$ 3
Staphylococcal bacteremia	0 (0)	0 (0)	1 (1)	1 (1)
Systemic candida	0 (0)	0 (0)	1 (1)	1 (1)
Tongue fungal infection	0 (0)	0 (0)	1 (1)	0 (0)
Urinary tract infection	1 (2)	0 (0)	6 (7)	5 (6)

Source: BLA 125463 Response to Information Request dated 6/28/2017 Table 2.5

Review Comment: Although there are no apparent differences in AEs by treatment without or with tocilizumab for CRS, the comparison is confounded by the high background rate of AEs due to the lymphodepleting chemotherapy and CRS, pooling of data for CRS prophylaxis and CRS treatment, and inclusion of all AEs without relation to timing of use of tocilizumab. Moreover, this limited analysis did not assess for infusion reactions, nor is it sufficient to exclude prolonged neutropenia or exacerbation of neurotoxicity in the patients treated with tocilizumab.

7.4.5 Analysis of Submission-Specific Safety Issues

No additional submission-specific issues were evaluated.

7.4.6 Safety Analyses in Related Intended Populations

Patients with SJIA have markedly elevated levels of inflammatory cytokines similar to patients with CAR T cell-induced CRS. Safety of tocilizumab in patients with SJIA has been reviewed previously (Coyle KM, Clinical Review of BLA 125276 S-022 dated 3/22/2011) for 112 patients 2 - 17 years of age with SJIA in Study WA18221 treated with tocilizumab at the proposed dose every 2 weeks for at least 12 weeks. The reviewer noted:

“Based on the known safety profile of TCZ in RA patients, in addition to previously identified risks of TCZ in SJIA patients (based on sJIA Chugai studies), primary AEs of interest included infections, macrophage activation syndrome (MAS), neutropenia, liver function test abnormalities, anaphylaxis and gastrointestinal perforation.

A higher overall AE rate was observed in sJIA patients than in RA patients. The SAE rate was also higher in sJIA patients than in RA patients. In both sJIA and RA patients, the death rate was <1.0 per 100 patient-years. The rate of premature treatment withdrawal for AE was lower in sJIA than in RA. The incidence of study drug dose modifications was similar in the two patient populations.

Infection AEs were the most frequent AEs in both sJIA and RA patient populations but were higher in sJIA patients than in RA patients (104 per 100 patient-years). The infection SAE rate was also higher in sJIA than in RA. In both pediatric patients with sJIA (based on study

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WA18221) and adult RA, <1 % of each patient population met the criteria of anaphylaxis according to the Sampson's analysis.

The incidence of MAS observed in WA18221, Chugai sJIA studies, and Chugai postmarketing surveillance (JPMS) studies was 2.7%, 2.7%, and 3.8%, respectively. These calculations compared favorably with the estimated background incidence of MAS between 6.8% and 8.2% in sJIA patients.

In WA18221, 13% and 2% of patients experienced CTC grade 3 and grade 4 neutropenia, respectively. 11 % and <1 % of patients experienced CTC grade 3 and grade 4 neutropenia, respectively, in Chugai sJIA studies. Compared with sJIA patients, CTC grade 3 and grade 4 neutropenia (<1 %) occurred less frequently in RA patients.

Grade 3 and 4 elevations in ALT/AST values were observed more often in sJIA treated with TCZ: grade 3 ALT: 7% in study WA18221 and 7% in Chugai studies; grade 3 AST: 0.9% in study WA18221 and 4% in Chugai studies; grade 4 ALT: none in study WA18221 and 2% in Chugai studies; grade 4 AST: 0.9% in study WA18221 and 1% in Chugai studies) in RA patients (grade 3 ALT: 3%, grade 3 AST: < 1 %, grade 4 ALT/ AST: 1 %).

In both pediatric patients with sJIA (based on study WA18221) and adult RA, < 1% of each patient population met the criteria of anaphylaxis according to the Sampson's analysis. No GI perforations were reported in study WA18221. One GI perforation was reported in the Chugai supportive studies (study MRA011JP), duodenal perforation was observed in one patient, a 10 year old male with sJIA."

There were no safety data submitted for use of tocilizumab for treatment of CRS induced by any therapeutic other than CAR T cells.

Review Comment: The results of WA18221 suggest that in the sJIA population with underlying active inflammation, cytopenias and liver test abnormalities may be increased after treatment with tocilizumab. To prevent serious toxicities from tocilizumab, the lowest number of doses that provide clinical benefit should be used. The lack of data that address safety in patients with CRS induced by any therapeutic other than CAR T cells will affect the recommended indication statement.

7.4.7 Specific Safety Studies/Clinical Trials

Study BP19461 was a single-center, randomized, double-blind, placebo-controlled, parallel-group study of single intravenous doses of tocilizumab in healthy adult volunteers. Safety testing was performed on study days 1, 2, 3, 4, 5, 8, 11, 15, 22, 29 and end of study, and adverse events were assessed through study day 50. Fifty-one subjects were randomized, and 36 subjects were treated. There were 10 subjects who received placebo and 26 subjects who received tocilizumab (5 at 2 mg/kg, 6 at 10 mg/kg, 10 at 20 mg/kg and 5 at 28 mg/kg).

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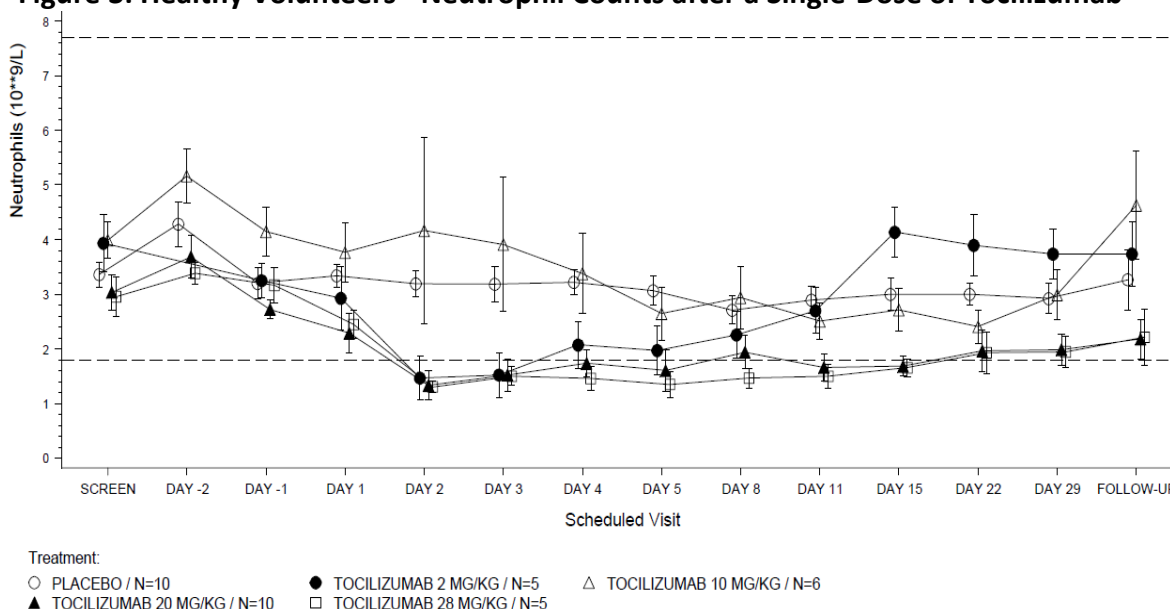
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There were no deaths, serious adverse events or AEs leading to withdrawal reported in this study. There were no substantial differences in incidences of AEs between placebo and active treatment, and there was no dose-related increase in the type, number or severity of AEs reported. The most common AEs experienced by subjects having received either tocilizumab or placebo were injection site reactions, headache, nasopharyngitis, pharyngolaryngeal pain and rhinorrhea. The majority of AEs in all groups were mild or moderate in intensity and considered by the investigator as unrelated or remotely related to study drug.

The main laboratory safety test abnormality was a decrease in neutrophil counts following administration of all doses of tocilizumab (Figure 3). Neutropenia is generally recognized to be associated with the IL-6 receptor blocking. The neutrophil counts nadired 1-2 days after tocilizumab administration and recovered thereafter but at end-of-study were still less than baseline for the 20 mg/kg and 28 mg/kg cohorts (Figure 3). The 20 mg/kg dose was considered the highest safe and tolerable dose.

Figure 3: Healthy Volunteers - Neutrophil Counts after a Single-Dose of Tocilizumab



Source: Study BP19461 Clinical Study Report Figure 5

Review Comment: From Figure 3 there appears to be a dose-related neutropenia. Neutropenia may pose a substantial risk for the patients with CAR T cell-induced CRS, but since the CRS generally occurs during the period of chemotherapy-induced myelosuppression, the risk may be mitigated by measures already in place. Prolonged neutropenia, however, could have devastating consequences in these patients, and this needs to be weighed against the risks of CRS being treated. The need to assess the risk and potential benefit for the individual patient must be clear in the Prescribing Information.

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7.4.8 Additional Safety Explorations

No additional safety explorations were performed.

7.4.9 Safety in the Postmarket Setting

The Periodic Safety Update Report (PSUR) 1072891 for the period 11 April 2016 to 10 October 2016 was reviewed. The following information was provided in this PSUR:

“The safety evaluation of the postmarketing data is consistent with the safety profile observed in the clinical trial data. The benefit-risk profile of tocilizumab for the treatment of RA (IV and SC formulations), sJIA, pJIA, and Castleman’s disease (IV formulation) remains unchanged and favorable. No additional updates to the CDS, RMP, or further actions are warranted at this time. The benefit-risk profile of tocilizumab has mainly remained unchanged since its approval despite the introduction of indications, routes, and age groups.

The known and potential risks of tocilizumab therapy include hypersensitivity reactions, infections, gastrointestinal perforation, malignancy, demyelination, immunogenicity, and laboratory abnormalities (neutropenia, thrombocytopenia, elevated liver transaminases, elevated lipids). The Actemra USPI includes a boxed warning for serious infections, warnings and precautions for serious infections, gastrointestinal perforations, hypersensitivity reactions, laboratory monitoring, and concomitant use of live vaccines, and dose modification instructions for serious infections and laboratory abnormalities.

These risks, with the exception of hypersensitivity reactions and infections, would generally be associated with long-term treatment and immune suppression with tocilizumab, and are unlikely to occur with one (or two doses) of tocilizumab.”

7.4.10 Integrated Assessment of Safety

There were no reports of deaths attributed to tocilizumab in the patients with CRS. In the CTL019 series, there were no adverse reactions attributed to tocilizumab. In the KTE-C19 series, there was no difference in the adverse reactions in patients who did or did not receive tocilizumab. The proposed doses of tocilizumab are supported by the safety profile in patients with SJIA. However, adverse reactions that might be unique in the CAR T cell-induced CRS population could not be evaluated with the data available, so some uncertainty persists regarding safety in this population. The Prescribing Information should be clear about the need to weigh the risks and potential benefits for individual patients being treated with tocilizumab.

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SUMMARY AND CONCLUSIONS

7.5 Statistical Issues

This application is based on pooling of selected patients from 5 independently conducted studies under BLA 125646 and 4 studies under BLA 125643. The pooling of data was not pre-specified in any of the study protocols. The dosing regimen and patient population varied among the studies. All analysis results for this application are descriptive.

7.6 Conclusions and Recommendations

The activity of tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg) for the treatment of severe or life-threatening CAR T-cell induced CRS is based on day-14 response as observed in retrospective analyses of two small series of clinical trials of CAR T cells. The literature review provides supporting evidence of activity. Uncertainty remains regarding the true response rate, since there was no randomized, concurrent or well-characterized historical control. The optimal dose and schedule are not well-established. The safety data in the intended population is quite sparse, but safety is supported by the extensive experience in a related population. The established risks of tocilizumab as well as the potential unique risks of tocilizumab can be mitigated through labeling. On the basis of the totality of the evidence, this review team recommends regular approval of tocilizumab for treatment of severe or life-threatening CAR T-cell induced CRS in adults and in pediatric patients 2 years of age and older. (b) (4)

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8 Advisory Committee Meeting and Other External Consultations

There is no Advisory Committee Meeting for this sBLA.

9 Pediatrics

Tocilizumab has Orphan Designation for “Treatment of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome” (August 1, 2017). Therefore, this submission is exempt from the pediatric assessment required under PREA.

The subgroup of patients selected for the analyses of efficacy of tocilizumab in this submission includes children as young as 3 years of age (Table 11). Prior reviews have established safety of the proposed tocilizumab dose down to the age of 2 years. Since both the pathogenesis of CAR T cell-induced CRS and the expected action of tocilizumab would be the same for a 2 year-old child as for those who are older, the efficacy of tocilizumab for this indication can be extrapolated to children 2 years old. Broadening the age limit for this indication further will be considered when safety data for infants is available.

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10 Labeling Recommendations

10.1 Prescribing Information

See final Actrema labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
1.5 Cytokine Release Syndrome		New indication
2.5 Dosage and Administration	If no clinical improvement in the signs and symptoms of CRS occurs (b) (4)	1. Changed to up to 3 additional doses of ACTEMRA may be administered. 2. Changed the interval between consecutive doses to at least 8 hours.
6.6 Clinical Trials Experience		A summary of the adverse events in a pooled data set for patients administered a tocilizumab dose of 8 mg/kg (12 mg/kg for patients less than 30 kg) was summarized.
8.4 Pediatric Use		The pediatric experience with ACTEMRA with CAR T cell-induced CRS was added.
14.6 Cytokine Release Syndrome-Intravenous Administration		The efficacy data of ACTEMRA for the treatment of CRS was added.

11 Risk Evaluation and Mitigation Strategies (REMS)

None.

12 Postmarketing Requirements and Commitments

Further characterize the safety of tocilizumab in the treatment of patients with chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome including the collection of data on the timing of tocilizumab administration relative to the nature and onset of adverse events. Submit the final data report and data set.

13 Appendices

13.1 References

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13.2 Financial Disclosure

See the reviews of BLA 125463 and BLA 125465 for the detailed assessments of financial conflict of interest.

13.3 Nonclinical Pharmacology/Toxicology

Not applicable.

13.4 OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1 Summary of Bioanalytical Method Validation and Performance

How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Free tocilizumab (not complexed to endogenous IL-6R) in human serum samples from Novartis Trial ELIANA was determined by electrochemiluminescence assay (ECLA). Test samples, quality controls, and standards (tocilizumab in buffer) were incubated on Streptavidin Gold plates pre-coated with Capturing Solution (500 ng/mL sIL-6R-BIOTIN), followed by washing with PBS and Tween. Bound samples were detected by incubation with Detection Solution (250 ng/mL sIL-6R-SULFOTAG). After the final wash step, Read Buffer T 2x is added to all the wells and ECL values which are in proportion to the bound SULFOTAG are measured at the Sector Imager. Analytical report was submitted for the use of the method in Trial ELIANA.

What bioanalytical methods are used to assess concentrations?

ECLA was used to measure free tocilizumab concentrations in human serum samples. The lower limit of quantitation (LLOQ) was 100 ng/mL and upper limit of quantitation (ULOQ) was 4000 ng/mL. Samples can be additionally diluted 200-fold with blank pooled human serum to quantification of tocilizumab concentrations up to, 200 times ULOQ, 800000 ng/mL. The bioanalytical method was validated in accordance with the US FDA Guidance for Industry “Bioanalytical Method Validation” (May 2001). The quantitative concentration ranges, storage conditions and developed ECLA method are appropriate to determine the tocilizumab concentration in human serum samples.

13.4.2 Clinical Pharmacokinetics

Tocilizumab samples were collected at pre-specified time-points (5-15 minutes, 24 hours $\pm$ 2 hours, and 48 hours $\pm$ 4 hours from first and second infusions) and quantified using validated ECLA assay in Novartis Trial ELIANA. The second dose of ACTEMRA was administered 2 days (min 0.5 day, max 4 days) after the first dose. Novartis submitted the preliminary, non-validated PK data from 27 patients in Trial ELIANA, and performed an exploratory non-compartmental analysis to determine the C_{max}. Other PK parameters could not be able reliably generated due to the sparse PK sampling schedule.

Tocilizumab PK concentration-time profiles for pediatric and adult patients with CAR T cell-induced severe or life-threatening CRS are depicted in **Figure 4**. As the proposed dose level for patients with CRS is 12 mg/kg for patients less than 30 kg weight or 8 mg per kg for patients at or above 30 kg weight, which is the same as the approved dose for patients with SJIA, the tocilizumab C_{max} was compared between these two patient populations (**Table 21**). The

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geometric mean (% CV) C_{max} in patients with CRS in Novartis Trial ELIANA was 99.5 $\mu\text{g/mL}$ (36.8%) following the first IV infusion dose ($n = 27$) and 161 $\mu\text{g/mL}$ (114%) following the second dose ($n = 8$), which is lower than observed geometric mean (% CV) C_{max} of 157 $\mu\text{g/mL}$ (74.2%) after the first dose and 262 $\mu\text{g/mL}$ (29.6%) at steady state in 75 pediatric patients with SJIA in Genentech Trial WA18221.

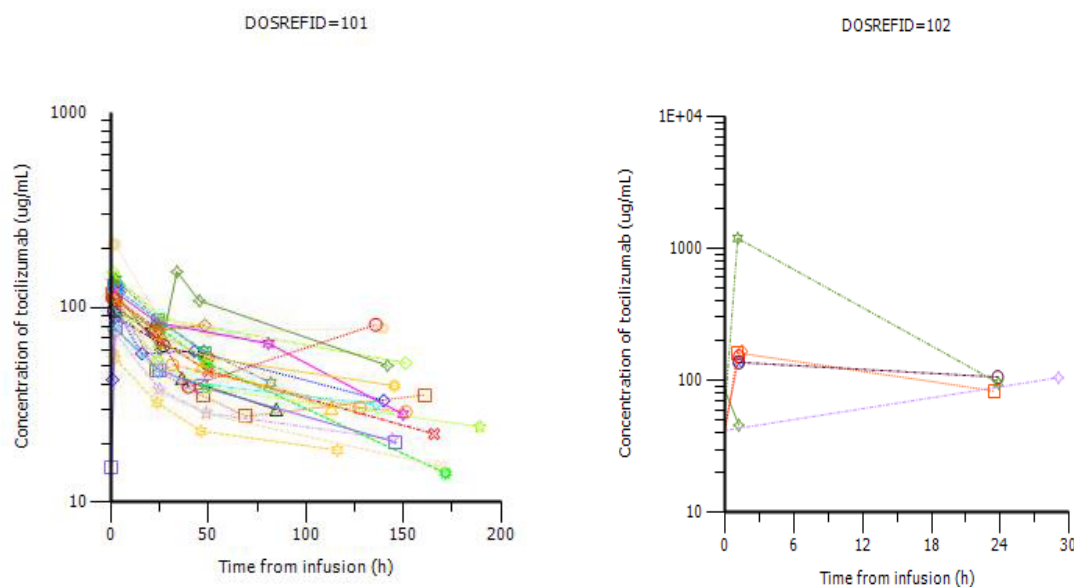


Figure 4: Tocilizumab PK Concentration-time Profiles in Pediatric and Young Adult Patients with CAR T Cell-induced Severe or Life-threatening CRS.

Source: Figure 3-1 in Novartis response to FDA request for information under BLA 125646.

DOSREFID=101: first dose of tocilizumab, DOSREFID=102: second dose of tocilizumab

Table 21: Comparison of Observed C_{max} after Tocilizumab Administration in Pediatric Patients with SJIA and Adult and Pediatric Patients with CAR T Cell-induced Severe or Life-threatening CRS.

Dosage regimen	Summary Statistics	Tocilizumab C_{max} ($\mu\text{g/mL}$)	
		CRS	SJIA
First Dose	N	27	74
	Mean $\pm$ SD	106 $\pm$ 35.8	181 $\pm$ 74.6
	Median [range]	111 [43.2, 210]	182 [12.2, 399]
	Geometric mean (%CV)	99.5 (36.8%)	157 (74.2%)
Steady state in SJIA, or second dose in CRS	N	8	75
	Mean $\pm$ SD	262 $\pm$ 377	272 $\pm$ 78.9
	Median [range]	146 [45.8, 1190]	268 [85.1, 547]
	Geometric mean (%CV)	161 (114)	262 (29.6%)

Source: CSR for Genentech Trial WQ18221 under BLA 125276 and Table 3-1 in Novartis response to FDA request for information under BLA 125646.

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13.4.3 Population PK Analysis

Neither Genentech nor Novartis conducted population PK analysis in patients with CAR T cell-induced severe or life-threatening CRS. Since there was no safety data available for tocilizumab in patients with CRS from any of the five Novartis trials or four Kite Pharma trials, population PK analysis serves as a critical approach to determine the dosage regimen for tocilizumab in patients with CAR T cell-induced severe or life-threatening CRS. Therefore, the reviewers conducted the following population PK modeling and simulation analyses to evaluate the appropriateness of the Sponsor proposed dosing regimen for tocilizumab in patients with CRS.

Objective

The objectives of reviewers' analysis are:

- To evaluate the predictive capability of the previous population PK model developed in patients with SJIA on PK data from patients with CRS;
- To refine a population PK model with the available PK data from patients with CRS if the previous population PK model could not describe well the PK data from patients with CRS;
- To simulate tocilizumab PK profiles after different dosage regimens based on the refined model to determine the acceptable dosing interval and total doses of tocilizumab in patients with CRS.

Methods

Datasets

The datasets used for modeling and simulations are summarized in **Table 22**.

Table 22: Analysis Datasets for modeling and simulations

Dataset	Name	Location
NONMEM dataset for Trial WA18221	NONMEM.xpt	\\cdsesub1\evsprod\bla125276\0025\m5\datasets\wa18221-pk\analysis\nonmem.xpt
PK parameters from Trial ELIANA	Appendix 1.csv	\\fdswf004\FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
PK concentrations from Trial ELIANA	Appendix 2.csv	\\fdswf004\FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
NONMEM dataset for Trial ELIANA	NONMEM_CRS.csv	\\fdswf004\FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Simulation dataset for four doses every 24 hours in patients with CRS	sim.dat.CRS.QD.MD.csv	\\fdswf004\FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Simulation dataset for four doses every 12 hours in patients with CRS	sim.dat.CRS.BID.MD.csv	\\fdswf004\FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Simulation dataset for four doses every 8 hours in patients with CRS	sim.dat.CRS.TID.MD.csv	\\fdswf004\FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses

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Software

NONMEM software (Version 7.3.0, Icon Development Solutions, Ellicott City, Maryland, USA)

(b) (4)
[REDACTED]) were used to develop population PK model and to generate the final individual PK parameters. (b) (4)

[REDACTED] were used for NONMEM dataset creation, goodness-of-fit (GOF) and visual predictive check (VPC) assessments.

Modeling and evaluation

The previous population PK model developed by Genentech using PK data from pediatric and young adult patients with SJIA in a European Trial LRO320 and a Japanese Trial MRA326 was applied to predict the PK data from patients with CRS. The previous population PK model was then refined to re-estimate linear clearance (CL) and volume of distribution in central compartment (V_C) using PK data from patients with CRS in Novartis Trial ELIANA. All the other parameters including inter-individual variabilities (IIV) of CL and V_C , as well as residual errors, were fixed to the previous PK parameters given the limited sparse PK observations from a small sample size of patients with CRS. The GOF and VPC assessments, decrease in objective function value (OFV), and the precision (% CV) of the parameter estimates were used for the model comparison and evaluation.

Simulations

The refined population PK model was then used for the determination of dosing interval and total doses of tocilizumab in patients with CRS. The following three simulation scenarios were repeated for 200 times to simulate median tendencies and 95% percentiles of PK time profiles as well as the corresponding 95% confidence intervals:

- a) Tocilizumab at proposed dose level once a day (QD) up to four doses;
- b) Tocilizumab at proposed dose level twice a day (BID) up to four doses;
- c) Tocilizumab at proposed dose level three times a day (TID) up to four doses.

For each simulation, 200 virtual individuals were sampled with replacement from 58 patients with CAR T cell-induced severe or life-threatening CRS with a median [min, max] age of 14 [3, 75] years old, a median [min, max] weight of 32 [10, 119] kg, a median [min, max] height of 132 [77, 184] cm, and a median [min, max] BSA of 1.07 [0.48, 2.39] m² in five Novartis trials (CTL019A2201, CTL019B2101J, CTL019B2102J, CTL019B2202 and CTL019B2205J).

Results

Predictive capability of previous population PK model

The previous population PK model developed in patients with SJIA was a two-compartment model with combined first-order and concentration dependent saturable elimination. The positive effects of BSA on CL, as well as age and height on V_C were described using power functions. The parameter estimates were summarized in **Table 23**. The VPC result (**Figure 5**) showed that PK observations in patients with CRS in Novartis Trial ELIANA generally fall within the simulated 95% prediction interval of PK time profiles after first dose and at steady state

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based on previous PK model. However, most of these observations were lower than simulated median tendency of the PK profiles, indicating the previous PK model may not be appropriate for the determination of dosage regimen in patients with CRS. It appears patients with CRS have faster tocilizumab clearance than those with SJIA.

Table 23: Summary of Population PK Parameters in Patients with SJIA from Trial MRA316 and Trial LRO320.

PK parameter	VALUE	SE	CI 5%	CI 95%
CL (L/day)	0.17	0.0079	0.15	0.19
Q (L/day)	4.6	0.43	3.8	5.4
V_c (L)	0.94	0.051	0.84	1
V_p (L)	1.6	0.085	1.4	1.8
Km (mg/L)	2.5	0	0	2.5
V_{max} (mg/day)	3.4	0.49	2.4	4.4
CL_BSA	0.99	0.087	0.82	1.2
V_c _HGT	2	0.23	1.5	2.5
V_c _Age	0.22	0.11	0.0044	0.44
Additive error (mg/L)	3.6	0.46	2.7	4.5
Multiplicative error (%)	15	1.2	13	17

SE-Standard error of estimates; CI-Confidence interval.

Source: Table 41 in Summary of Clinical Pharmacology Studies under BLA 125276.

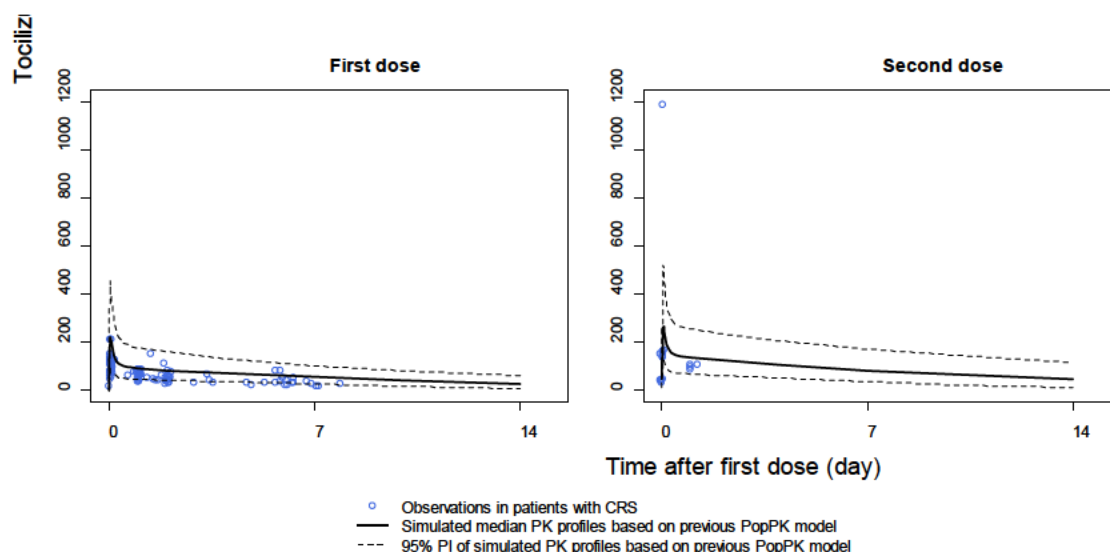


Figure 5: Visual Predictive Check Performed with the Previous PK Model in Patients with SJIA for the Tocilizumab Serum Concentrations in Patients with CRS.

Source: Reviewers' analysis.

Model refinement and validation

The key runs of the model refinement are summarized in Table 24. As a starting point, the previous population PK model with all fixed parameters in patients with SJIA (run004) was re-run using 125 PK observations after first and second tocilizumab doses from 27 patients with CRS. Three different models were tested to re-estimate CL or V_c separately, and both of them together:

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- run005: fixed all parameters except CL
- run006: fixed all parameters except V_c
- run007: fixed all parameters except CL and V_c

The best model for patients with CRS was found to be model run007 with re-estimated CL and V_c . The OFV significantly ($p < 0.001$) decreased by 95.2 as compared to the previous PK model (run004). GOF plots of the refined model (run007) are presented in **Figure 6**. The plots show a random and equal distribution of the observed versus population and individual predicted concentrations around the line of identity. Conditional weighted residuals (CWRES) are randomly distributed around 0 when plotted over time after dose or population predicted concentrations. **Figure 7** presents the VPC result by comparing the 95% prediction interval of the simulated tocilizumab concentrations with the observed concentrations in patients with CRS. The model appears to describe the median tendency and overall variability of the observed data adequately. Individual concentration-time plots showed the refined PK model could fit the observed data well after both first and second tocilizumab doses in patients with CRS (**Figure 8**). CL was estimated to be 0.50 L/day (RSE = 10.8%) and V_c was estimated to be 1.8 L (RSE = 11.2%) in patients with CRS, which were higher than CL of 0.17 L/day and V_c of 0.94 L in patients with SJIA.

As the tocilizumab serum concentrations in patients with CRS have not been validated by Novartis yet, an observation of 1190 $\mu\text{g/mL}$ after the second dose in patient ID = 24, which was much higher (> 5 -fold) than other observations in all 27 patients, seems to be a potential outlier. A sensitivity analysis (model run008) was conducted to evaluate the impact of this observation on parameter estimation. The sensitivity analysis showed that deleting this observation (model run008) did not significantly alter the estimates of CL (0.49 L/day vs. 0.50 L/day) and V_c (2.0 L vs. 1.8 L) as compared to model run007. Therefore, model run007 was selected as the final refined PK model for the following simulation procedures.

Table 24: Summary of Key Runs during Refinement of Population PK Model

#Run	#Ref	Description	Dataset	OFV	ΔOFV	Min.	COV	Sign.
Previous population PK model in SJIA								
001		2-compartment model with combined first-order and concentration dependent saturable elimination, BSA on CL, age and height on V_c , IIV for CL and V_c	NONMEM.csv	6642.7				
Model refinement for patients with CRS								
004	001	2-compartment model with combined first-order and concentration dependent saturable elimination, BSA on CL, age and height on V_c , IIV for CL and V_c	NONMEM_CRs.csv	1090.3		Successful	OK	
005	004	Re-estimation of CL	NONMEM_CRs.csv	1029.1	-61.2	Successful	OK	4.9
006	004	Re-estimation of V_c	NONMEM_CRs.csv	1058.9	-31.4	Successful	OK	3.6
007	004	Re-estimation of CL and V_c	NONMEM_CRs.csv	995.1	-95.2	Successful	OK	4.2
008	007	Sensitivity analysis, ignore an outlier from patient ID = 24	NONMEM_CRs.csv	900.9	-94.2	Successful	OK	3.3

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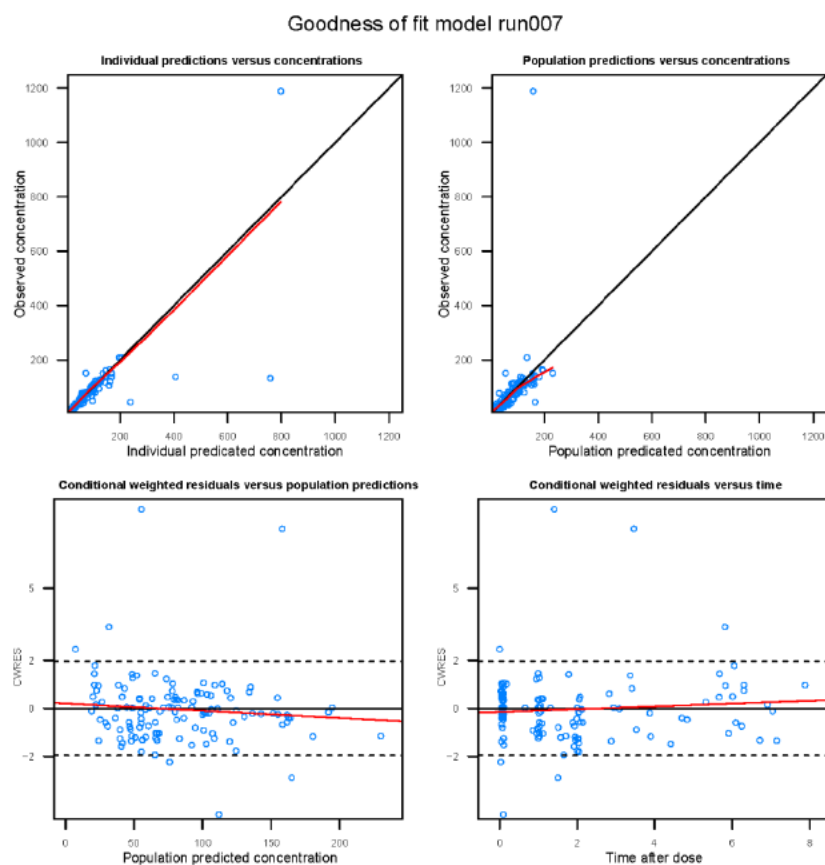


Figure 6: Goodness-of-fit Plots of the Refined PK Model.

Source: Reviewers' analysis.

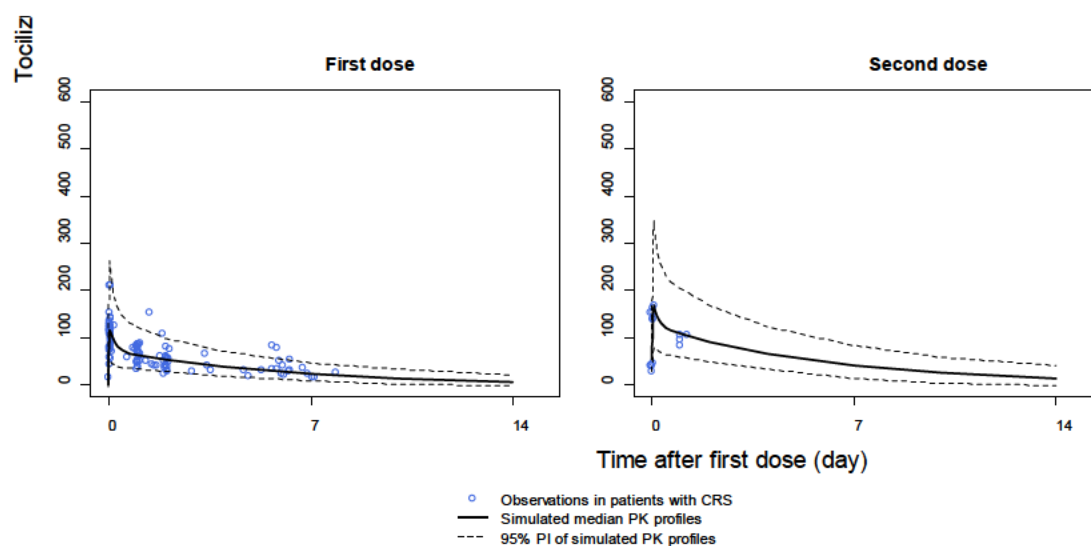


Figure 7: Visual Predictive Check Performed with the Refined PK Model for the Tocilizumab Serum Concentrations after First and Second Doses in Patients with CRS.

Source: Reviewers' analysis.

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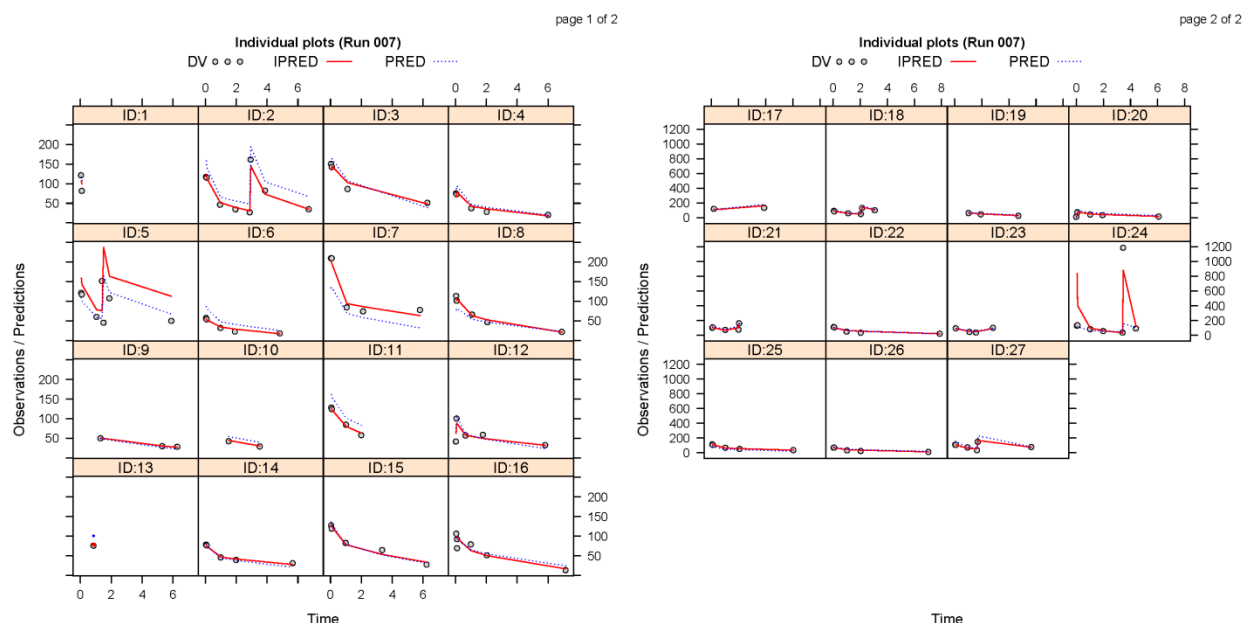


Figure 8: Individual Observed and Simulated Tocilizumab Serum Concentration-time Profiles after First and Second Doses in Patients with CRS.

Source: Reviewers' analysis.

Simulations based on refined model

Figure 1 shows the median tendencies and the corresponding 2.5th and 97.5th percentiles of simulated PK time profiles after four tocilizumab doses of 12 mg/kg (<30 kg weight) or 8 mg/kg (≥ 30 kg weight) via IV infusion over 1 hour every 24 hours, 12 hours or 8 hours in adult and pediatric patients 2 years of age and older with CAR T cell-induced severe or life-threatening CRS. Tocilizumab serum concentrations tend to accumulate more quickly with the increasing dosing frequency for a total of four doses given the nonlinear PK characteristics of tocilizumab. The simulated median (2.5th, 97.5th percentiles) of tocilizumab C_{max} was 259 µg/mL (131 µg/mL, 495 µg/mL) after four IV infusion doses administered every 24 hours, 295 µg/mL (144 µg/mL, 567 µg/mL) every 12 hours, and 312 µg/mL (151 µg/mL, 606 µg/mL) every 8 hours in 200 virtual patients with CRS. Overall, the simulated tocilizumab concentrations after four IV infusion doses, whether the doses were administered every 24 hours, 12 hours or 8 hours, were generally below the observed highest C_{max} of 649 µg/mL in five healthy subjects after a single dose of 28 mg/kg in Trial BP19461. Therefore, a total of four tocilizumab doses of 12 mg/kg for patients less than 30 kg weight or 8 mg/kg for patients at or above 30 kg weight with a dosing interval of at least 8 hours is acceptable for adult and pediatric patients 2 years of age and older with CAR T cell-induced severe or life-threatening CRS.

Conclusion

Based on the independent population PK analysis conducted by the reviewers, we agree with the Sponsor's proposed ACTEMRA dose level of 12 mg/kg (< 30 kg weight) or 8 mg/kg (≥ 30 kg weight) for adult and pediatric patients 2 years of age and older with CAR T cell-induced severe or life-threatening CRS. However, we propose up to 3 additional doses of ACTEMRA with a

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dosing interval of at least 8 hours between consecutive doses if no clinical improvement in the signs and symptoms of CRS occurs after the first dose.

Listing of analyses codes and output files

File Name	Description	Location
Run007.mod	Control stream for the final refined PK model	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Run007.lst	NONMEM output for the final refined PK model	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Run105.mod	Control stream for simulation of PK profiles after first dose in patients with CRS	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Run106.mod	Control stream for simulation of PK profiles after second dose in patients with CRS	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Run121.mod	Control stream for simulation of PK profiles after 4 doses every 24 hours in patients with CRS	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Run122.mod	Control stream for simulation of PK profiles after 4 doses every 12 hours in patients with CRS	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Run123.mod	Control stream for simulation of PK profiles after 4 doses every 8 hours in patients with CRS	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses
Population analysis.R	R code to generate NONMEM datasets, GOF plots, VPC plots, etc.	\\fdswf004\#FDSWF004\DCP5\$\Workload\DHP teams\Liang Li\BLA125276-S114\PopPK Analyses\Pirana codes

13.4.4 Exposure-Response Analyses

Not applicable. Genentech, Novartis or Kite Pharma did not conducted exposure-response analysis for efficacy or safety measurements in patients with CAR T cell-induced severe or life-threatening CRS.

BLA Multidisciplinary Review and Evaluation

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14 Division Director (DHOT)

Not applicable.

BLA Multidisciplinary Review and Evaluation

BLA 125276 S-114

Actemra (tocilizumab)

15 Division Director (OCP)

Nam Atiqur Rahman, PhD

Division Director (OCP)

BLA Multidisciplinary Review and Evaluation

BLA 125276 S-114

Actemra (tocilizumab)

16 Division Director (OB)

Thomas Gwise, PhD

Deputy Division Director (OB/DBV)

BLA Multidisciplinary Review and Evaluation

BLA 125276 S-114

Actemra (tocilizumab)

17 Division Director (DHP)

As noted above, the review team recommends regular approval of tocilizumab under 21 CFR 601 for the indication “for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older.” I concur with this recommendation for this potentially fatal syndrome which is based on a retrospective data analysis from two submitted BLAs for CAR T cell products. The team’s analysis demonstrated that 69% of patients with CAR T cell-induced severe or life-threatening cytokine release syndrome had resolution of fever and need for vasopressors within days of 1 or 2 doses of tocilizumab. Due to the nature of how adverse reactions were collected in the two CAR T cell BLAs, further study is required to confirm the safety of tocilizumab in the intended population.

Tocilizumab approval for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome is an outstanding example of pharmaceutical cooperation and data sharing among pharmaceutical sponsors to benefit patients with a potentially fatal syndrome.

Ann T. Farrell, M.D.

Director, Division of Hematology Products (DHP)

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/s/

NATASHA L KORMANIK
08/28/2017

ROBERT Q LE
08/28/2017

LIANG LI
08/29/2017

BAHRU A HABTEMARIAM
08/29/2017

STACY S SHORD
08/29/2017

NAM ATIQUR RAHMAN
08/29/2017
I concur.

WEISHI YUAN
08/29/2017

LEI NIE
08/29/2017

THOMAS E GWISE
08/29/2017

DONNA PRZEPIORKA
08/29/2017

ANN T FARRELL
08/29/2017

MEMORANDUM

TO: File for BLA 125276

FROM: Pedro L. Del Valle, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

THROUGH: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

DATE: August 22, 2016

SUBJECT: Recommend Approval of BLA S-114

Actemra (tocilizumab) was approved on January 08, 2010 and it is indicated for the treatment of Adult Rheumatoid Arthritis (RA), Systemic Juvenile Idiopathic Arthritis (SJIA), Polyarticular Juvenile Idiopathic Arthritis (PJIA), and Giant Cell Arteritis (GCA). The Applicant (Genentech Roche) submitted an efficacy supplement for a new indication for Actemra for the treatment of patients with severe or life-threatening cytokine release syndrome (CRS) in patients 5 years of age and older.

The proposed PI was reviewed by the Division of Hematology Products (DHP) and the Division of Medication Error Prevention and Analysis (DMEPA). No updates were proposed for pharmacology/toxicology Sections 8 and 13 of the PI. There are no outstanding issues from a pharmacology/toxicology perspective regarding the approval of this supplement.

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/s/

PEDRO L DEL VALLE

08/22/2017

CHRISTOPHER M SHETH

08/22/2017

BLA Supplement - Clinical Reviewer Memo
Division of Hematology Products

BLA	125276 S-114
Submission Type	BLA Efficacy Supplement
Applicant	Genentech
Submission Date	6/1/2017
Proper Name	Tocilizumab
Trade Name	Actemra
Clinical Reviewer	Robert Q. Le, MD, PhD
Clinical Team Leader	Donna Przepiorka, MD, PhD

The clinical review is incorporated into the Multidisciplinary Review and Evaluation. The recommended regulatory action is regular approval.

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/s/

DONNA PRZEPIORKA
08/22/2017

ROBERT Q LE
08/22/2017

Office of Clinical Pharmacology Memo

NDA or BLA Number	BLA 125276						
Link to EDR	\\CDSESUB1\evsprod\BLA125276\0244						
Applicant	Genentech, Inc.						
Submission Date	06/01/2017						
Submission Type	Efficacy supplement						
Brand Name	ACTEMRA®						
Generic Name	Tocilizumab						
Dosage Form and Strength	Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion						
Route of Administration	Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.						
Proposed Indication	Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS).						
Proposed Dosing Regimen	The recommended dose of ACTEMRA for treatment of CRS given as a 60-minute intravenous infusion is: <table border="1"> <thead> <tr> <th colspan="2">Recommended Intravenous CRS Dosage</th></tr> </thead> <tbody> <tr> <td>Patients less than 30 kg weight</td><td>12 mg per kg</td></tr> <tr> <td>Patients at or above 30 kg weight</td><td>8 mg per kg</td></tr> </tbody> </table> - If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of ACTEMRA may be administered. The interval between consecutive doses should be at least 8 hours. - Subcutaneous administration is not approved for CRS.	Recommended Intravenous CRS Dosage		Patients less than 30 kg weight	12 mg per kg	Patients at or above 30 kg weight	8 mg per kg
Recommended Intravenous CRS Dosage							
Patients less than 30 kg weight	12 mg per kg						
Patients at or above 30 kg weight	8 mg per kg						
Associated IND	IND (b) (4)						
OCP Review Team	Liang Li, Ph.D.; Bahru Habtemariam, Pharm.D.; Stacy Shord, Pharm.D.						
OCP Final Signatory	Stacy Shord, Ph.D. Team Leader Division of Clinical Pharmacology V						

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Based on our analyses of the submitted PK, efficacy, and safety data, tocilizumab is approvable for adults and pediatric patients 2 years of age and older with CAR T cell-induced severe or life-threatening CRS from a clinical pharmacology perspective.

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/s/

LIANG LI
08/22/2017

BAHRU A HABTEMARIAM
08/22/2017

STACY S SHORD
08/22/2017