28 June 2018
EMA/491183/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0078

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ACR	American College of Rheumatology
BW	body weight
CHAQ-DI	Childhood Health Assessment Questionnaire-DisabilityIndex
CFB	change from baseline
CI	confidence interval
CSR	clinical study report
DMARD	disease-modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
ILAR	International League of Associations for Rheumatology
ITT	intent to treat
IV	Intravenous
JADAS-71	Juvenile Arthritis Disease Activity Score 71
JIA	juvenile idiopathic arthritis
LOCF	last observation carried forward
LTE	long-term extension
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
SAS	Safety Analysis Set
SC	subcutaneous
SCE	summary of clinical efficacy
SDS	standard deviation score
sJIA	systemic juvenile idiopathic arthritis
TCZ	tocilizumab
TNF	tumour necrosis factor
VAS	visual analog scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 22 May 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the indication 'treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older' for the RoActemra 20mg/ml concentrate for solution for infusion. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 the SmPC are updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0181/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred. Partial compliance check has been completed. The PIP P/0266/2015 of 19/11/20115 was completed.

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	22 May 2018
Start of procedure	30 May 2018
CHMP Rapporteur Assessment Report	13 June 2018
CHMP members comments	18 June 2018
Updated CHMP Rapporteur Assessment Report	28 June 2018
Opinion	28 June 2018

2. Scientific discussion

2.1. Introduction

About the product

Tocilizumab (TCZ) is a recombinant humanised anti-human IgG1 monoclonal antibody directed against the interleukin-6 receptor (IL-6R) that binds specifically to both soluble and membrane-bound IL-6R, thereby inhibiting IL-6-mediated signalling.

Interleukin 6 (IL-6), the ligand of IL-6R, is a cytokine produced by a wide variety of cells in the human body. Its normal role is primarily to regulate hematopoiesis, to stimulate immune responses, and to mediate acute phase reactions. Consequently, excessive production of IL-6 can be implicated in the pathogenesis of several diseases involved with these functions, such as rheumatoid arthritis (RA), multiple myeloma and Castleman's Disease. IL-6 exerts its biological effects through both the membrane bound IL-6 receptor (mIL-6R), and the soluble form of the receptor (sIL-6R). TCZ binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. TCZ has been shown to inhibit the biological activities of IL-6 in vitro and in vivo, and to suppress the development of arthritis and C-reactive protein synthesis in a collagen induced arthritis model in cynomolgus monkey.

TCZ is available in 2 different pharmaceutical forms to allow either administration by intravenous (IV) infusion or by subcutaneous (SC) injection. Both pharmaceutical forms of TCZ are approved in the EU, in combination with methotrexate (MTX), for the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults, for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis). The SC formulation of TCZ is also approved in the EU for the treatment Giant Cell Arteritis (GCA) in adult patients. The IV formulation of TCZ is also approved in the EU for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older.

Problem statement

Cytokine release syndrome has been identified as a potentially life-threatening significant on-target side-effect of cancer immunotherapies designed to stimulate the immune system to attack tumour cells, including T-cell-recruiting agents such as the CD19-directed CAR T-cell therapies axicabtagene ailoleucel and tisagenlecleucel-T. The reported incidence of CRS following CAR T-cell therapy ranges from 50% to 100% (any CTCAE grade), with 10% to 65% of patients experiencing severe or life threatening CRS.

Cytokine release syndrome

Cytokine release syndrome (CRS) is caused by the excessive release of cytokines by immune effector or target cells during an exaggerated immune response. CRS can be triggered by infections or by therapeutic interventions, which activate the immune response, with the severity of CRS most likely related to the degree and duration of immune activation.

The reported incidence of CRS following CAR T-cell therapy ranges from 50% to 100% (any CTCAE grade), with 10% to 65% of patients experiencing severe or life threatening CRS. CRS has also been associated with the CD19/CD3 bispecific antibody blinatumomab (Blincyto SmPC), and also nonspecific T-cell agonists such as TGN1412 targeting CD28 and OKT3 targeting CD3. Cancer immunotherapy driven CRS may also result from lysis of tumour cells (e.g., rituximab, obinutuzumab), which clinically manifests as infusion reactions. Finally, therapies that block inhibitory signals to T-cells (e.g., checkpoint inhibitors) could also theoretically result in CRS or could exacerbate CRS if given in combination with other cancer immunotherapies. The clinical signs and symptoms of CRS following cancer immunotherapy can vary across patients but are similar regardless of the inciting agent. Most patients present with mild or moderate flu-like symptoms, including fever, nausea, headache, chills, and myalgia, which are easily managed. However, some patients experience more severe, life-threatening signs and symptoms, including hypotension, tachycardia, dyspnoea, vascular leak, pulmonary oedema, and disseminated intravascular coagulopathy, as a result of massive cytokine release. Such severe reactions are marked by their rapid onset and require emergency treatment to prevent potentially life-threatening complications such as cardiac dysfunction, acute respiratory distress syndrome, and multi-organ failure.

Table 1 Clinical signs and symptoms of CRS

Organ System	Clinical Signs and Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia [a]
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

Reproduced from Lee et al. 2014a.

a Pulmonary edema can also occur.

The severity of CRS has been defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading system based on the requirement for and response to

treatment (Table 2). This grading system applies to all CRS events regardless of inciting agent but was based on grading of acute infusion-related toxicities caused by monoclonal antibodies and is not necessarily applicable for CRS events arising with cancer immunotherapy (Recombinant DNA Advisory Committee Meeting, 2015). Revised grading systems have been proposed for CRS occurring in the setting of cancer immunotherapy.

Table 2 NCI – CTC for AEs: CRS

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild reaction Infusion interruption not indicated Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids) Prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) Recurrence of symptoms following initial improvement Hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences Pressor or ventilatory support indicated	Death

Source: NCI CTCAE version 4.0, published May 28, 2009 (v4.03: June 14, 2010).

Management of CRS

Prophylaxis to reduce the incidence and severity of CRS is recommended prior to administration of some medications, including blinatumomab (Blincyto) muronomab-CD3 (Orthoclone OKT3) and rituximab (MabThera). Premedication with corticosteroids, antihistamines and acetaminophen, in addition to other measures, such as slowing down the infusion and fractionated dosing, can help manage events (Bugelski et al. 2009). However, severe and life-threatening CRS can still occur even after these precautionary measures have been taken. In addition, in some circumstances, premedication is not favoured due to concerns it may reduce the efficacy of the primary medication, for example, administration of corticosteroids that can have deleterious effects on immune cell function (Davila et al. 2014; Lee et al. 2014a).

Treatment of CRS primarily focuses on rapidly reducing the excessive inflammatory response by use of IV corticosteroids and antihistamines, and treating the individual signs and symptoms of CRS, 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. There is currently no authorised medicine available in the EU specifically for the treatment of CAR-T cell-induced CRS.

Severe or life-threatening CRS is a medical emergency and if unsuccessfully managed, can result in significant morbidity or mortality. However, treatment of these events is challenging, as they do not always respond to conventional treatment, especially in the case of late intervention. As such, there is a high unmet medical need for a more effective treatment to manage CRS, particularly the more severe reactions. As CRS is associated with excessive levels of circulating cytokines, anti-cytokine therapy has been investigated as a potential treatment for CRS, particularly for severe or life-threatening reactions. Published small series or case reports of several anti-cytokine therapies to treat CRS have yielded mixed results (Grupp et al. 2013, 2015; Bruck et al. 2011; Kelly and Ramanan 2008; Pachlopnik, Schmid et al. 2009).

There has been an increase in reports of TCZ being used by physicians to successfully treat severe or life-threatening CRS, and it has been authorised in the US for this purpose (Le et al. 2018).

Emerging evidence suggests that the cytokine IL-6 is the central mediator of toxicity in CRS, and IL-6R blockade using TCZ has been shown to be highly effective in treating patients with severe or life-threatening CRS, particularly in patients treated with immune agonist anti-cancer therapy including agents designed to recruit T-cells to tumours. Specifically, as a result of published data demonstrating the efficacy of TCZ to treat severe CRS following administration of T-cells engineered to express chimeric antigen receptors (CARs), TCZ is being increasingly used by physicians to treat CRS caused by immune-directed therapies and is becoming standard medical practice in many institutions (Lee et al. 2014a).

CRS in CAR-t therapies

CRS has been identified as a significant on-target side-effect of chimeric antigen receptor (CAR) T-cell therapies, including T-cell-recruiting agents such as the CD19-directed CAR T-cell therapies axicabtagene ciloleucel (Yescarta/KTE-C19) and tisagenlecleucel (Kymriah/CTL019), which have been subject to assessment by the CHMP for the treatment of haematological malignancies. Scientific literature suggests that Tocilizumab has been successfully used to treat patients who developed CRS in those studies (Grupp et al. 2016; Locke et al. 2017).

The proposed extension of indication aims to include the indication 'treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older' for the RoActemra 20mg/ml concentrate for solution for infusion.

The recommended posology for treatment of CRS given as a 60-minute intravenous infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. RoActemra can be given 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 RoActemra may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

As tocilizumab is a protein it is unlikely to pose any environmental risk therefore ERA studies for tocilizumab are exempted in accordance with the ERA guideline EMA/CPMP/SWP/4447/00.

2.3. Clinical aspects

2.3.1. Introduction

This application for this Type II variation rests on the clinical data relevant to patients treated with tocilizumab following the administration of CAR-T cell therapies. The current application is further substantiated on the basis of published data (either full-text manuscripts or conference abstracts) describing the effectiveness of tocilizumab in treating severe or life-threatening CRS.

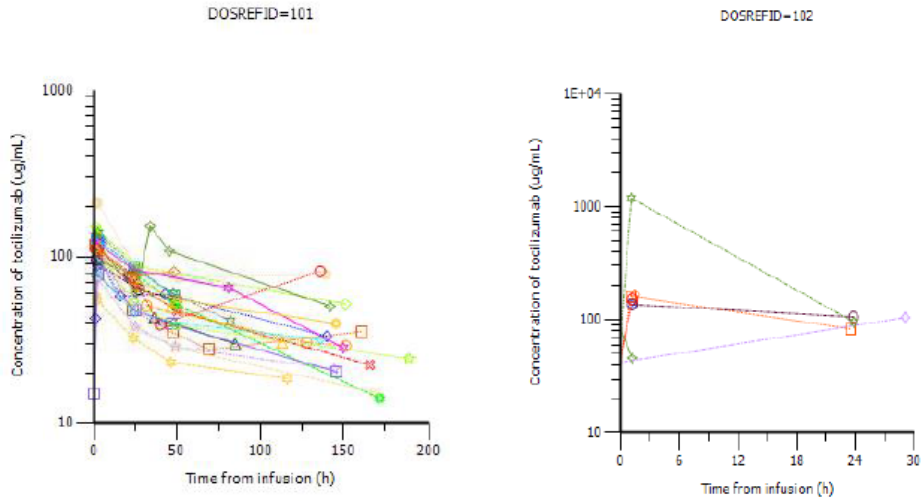
2.3.2. Pharmacokinetics

Based on the analysis of TCZ/CRS data from the CAR T-cell trials, pharmacokinetics (PK) data were available for 27 patients after the first dose of TCZ and for 8 patients after a second dose of TCZ. The PK population included 15 male and 12 female patients of median age 12 years (range, 4-23 years). The geometric mean (% CV) maximum concentration of TCZ in the patients with CAR T-cell-induced, severe or life-threatening CRS was 99.5 μg/mL (36.8%) after the first infusion and 160.7 μg/mL (113.8%) after the second infusion. Using a refined population PK model, simulations were performed by FDA for the recommended TCZ dose given every 8, 12, or 24 hours.

Free tocilizumab (not complexed to endogenous IL-6R) in human serum samples from Novartis Trial ELIANA was determined by electro-chemiluminescence assay (ECLA). Tocilizumab samples were collected at pre-specified time-points (5-15 minutes, 24 hours ± 2 hours, and 48 hours ± 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 reliably generated due to the sparse PK sampling schedule.

Tocilizumab PK concentration-time profiles for paediatric and adult patients with CAR T cell induced severe or life -threatening CRS are depicted below.

Figure 1: Tocilizumab PK concentration-time profiles in paediatric and young adult patients with CAR T Cell-induced severe or life-threatening CRS.



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. The geometric mean (% CV) C_{max} in patients with CRS in Novartis Trial ELIANA was 99.5 μg/mL (36.8%) following the first IV

infusion dose (n = 27) and 161 µg/mL (114%) following the second dose (n = 8), which is lower than observed geometric mean (% CV) C_{max} of 157 µg/mL (74.2%) after the first dose and 262 µg/mL (29.6%) at steady state in 75 paediatric patients with SJIA.

Table 3: Comparison of observed C_{max} after tocilizumab administration in paediatric patients with SJIA and adult and paediatric patients with CAR T cell-induced severe or life-threatening CRS.

Dosage regimen	Summary Statistics	Tocilizumab Cmax (µg/mL)	
		CRS	SJIA
First Dose	N	27	74
	Mean ± SD	106 ± 35.8	181 ± 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 ± SD	262 ± 377	272 ± 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.

The following population PK modelling and simulation analyses to evaluate the appropriateness of the proposed dosing regimen for tocilizumab in patients with CRS were conducted. The previous population PK model developed using PK data from paediatric 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 (VC) using PK data from patients with CRS in Novartis Trial ELIANA. All the other parameters including inter-individual variabilities (IIV) of CL and VC, 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.

Figure 2: Visual predictive check performed with the previous PK model in patients with SJIA for the tocilizumab serum concentrations in patients with CRS.

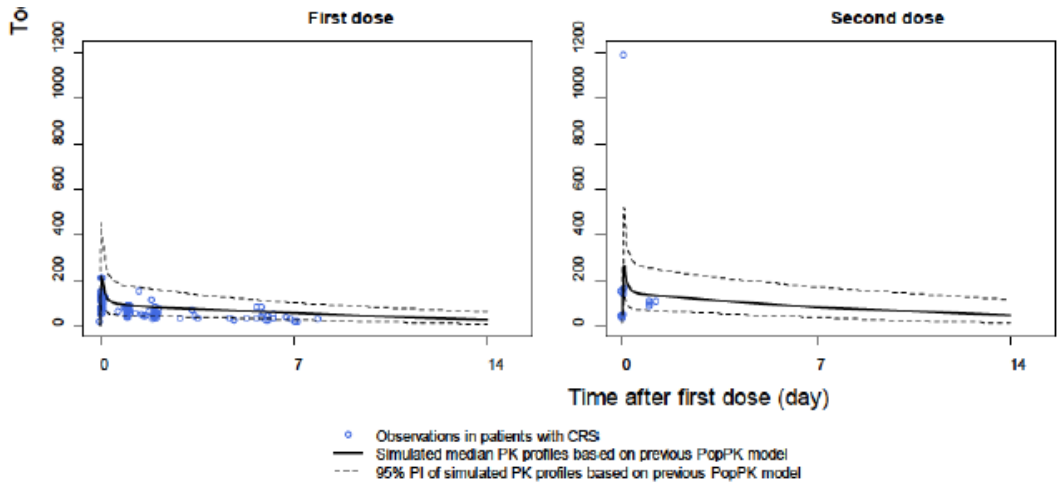


Figure 3: Goodness of fit plots of the refined PK model.

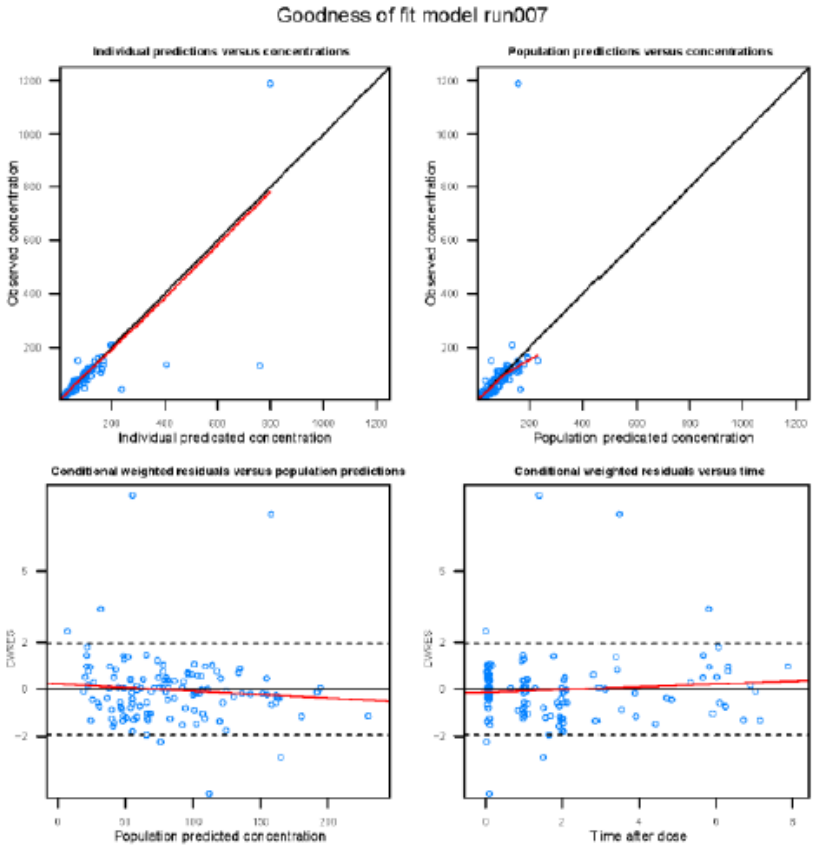


Figure 4: Individual observed and simulated serum concentration-time profiles after first and second doses in patients with CRS.

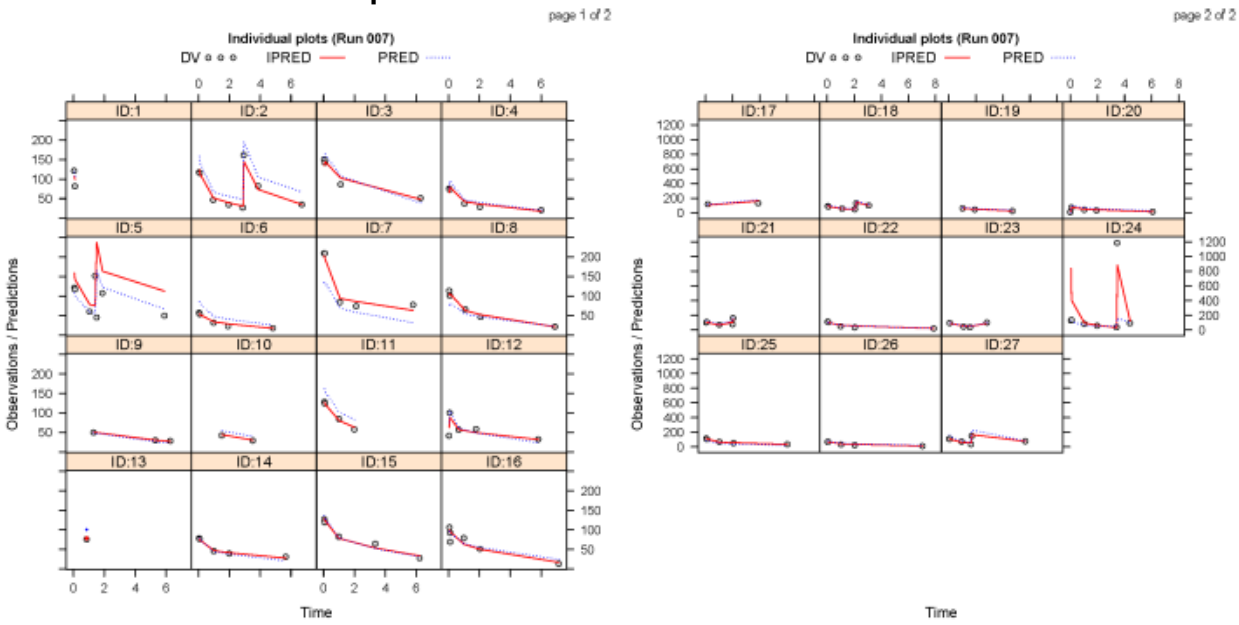


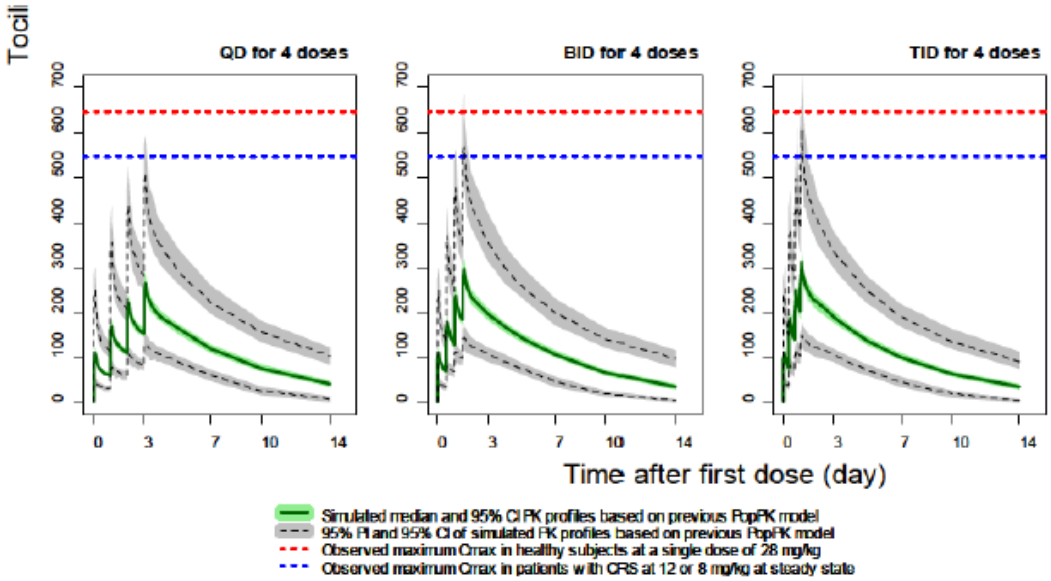
Figure 8: Individual Observed and Simulated Tocilizumab Serum Concentration-time Profiles after First and Second Doses in Patients with CRS.

Source: Reviewers' analysis.

The figure below 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 paediatric 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.

Figure 5: Simulated 2.5th 50th and 97.5th percentiles and corresponding 95% CI of tocilizumab PK profiles in patients with CAR-T cell induced severe or life threatening CRS after 4 doses every 24h (left), 12h (middle), or 8h (right panel) in CRS patients.



Study BP19461 (evaluation of the safety of supra-therapeutic doses of RoActemra)

Study BP19461 consisted of a Part 1 (an evaluation of the safety of supra-therapeutic doses following single doses in healthy subjects) and a Part 2 (an evaluation of the effect on QT interval following single doses in healthy subjects) and aimed to investigate the safety and tolerability of tocilizumab at supra-therapeutic doses in healthy subjects in order to support the dose selection for part 2 of the study (thorough QT study) and to investigate the pharmacokinetics (PK) of tocilizumab at supra-therapeutic doses in healthy subjects.

The PK of tocilizumab was characterised by nonlinear kinetics over the dose range tested. CL was concentration-dependent. There was no deviation from a dose proportional increase for C_{max} ($p = 0.168$ for deviation from dose proportionality); and a more than dose proportional increase in AUC_{inf} after doses of 2 to 28 mg/kg ($p < 0.0001$ for deviation from dose proportionality). The over-proportional increase in AUC_{inf} with increasing dose seemed more pronounced between the 2 and 10 mg/kg doses than between the higher doses (10, 20 and 28 mg/kg). The highest systemic exposures to tocilizumab were achieved with the 28 mg/kg dose, with mean AUC_{inf} and C_{max} values of 147000 h*µg/mL and 558 µg/mL, respectively. Mean CL was estimated as 0.609 mL/h/kg for the 2 mg/kg dose and decreased with increasing doses to 0.192 mL/h/kg for the highest dose of 28 mg/kg. Mean t1/2 ranged from 54 hours after 2 mg/kg to 293 hours after 28 mg/kg. Mean V_{ss} ranged from 50.0 (2 mg/kg) to 85.7 mL/kg (20 mg/kg). Median t_{max} was between 3 and 4 hours for all doses investigated.

Single doses of 2, 10, 20 and 28 mg/kg of tocilizumab were well tolerated. No unexpected safety findings were observed. Although the 28 mg/kg dose was associated with no immediate safety issues, the potential implications of decreases in neutrophils over a prolonged period of time with this dose precluded

its selection for part 2 of the study. The 20 mg/kg dose was considered the highest safe and tolerable dose to be administered to a large group of healthy volunteers in the thorough QT part of the study.

Exposure – response relationship

Table 4: List of IV TCZ studies and associated C_{max} in adults with PK endpoints

Disease population	Study number	N	Duration / Dose	*C_{max} (µg / ml)
HV	BP19461		Single Dose:	
		5	2 mg/kg	41.9± 3.33
		6	10 mg/kg	242± 31.3
		10	20 mg/kg	410± 81.3
		5	28 mg/kg	558± 79.2
		30	10 mg/kg	208 (143-310)
			20 mg/kg	419 (340-496)
HV, Japanese	MRA001JP	28	Single Dose:	
			0.15 mg/kg	2.4± 0.61
			0.5 mg/kg	8.49± 1.17
			1 mg/kg	19.5± 2.73
			2 mg/kg	37.6± 8.78
RA, Japanese	LRO300	45	Single Dose:	
			0.1 mg/kg	1.96± 1.26
			1 mg/kg	17.9± 4.7
			5 mg/kg	123± 21
			10 mg/kg	273± 121
RA, Japanese	MRA002JP	15	Multiple Dose:	
			2 mg/kg	27.9± 12.3
			4 mg/kg	49.5± 10.1
			8 mg/kg Q2W	130± 48.1
HV, Japanese	MRA004JP	6	Single Dose: 2 mg/kg	26.4 ± 5.78
Castleman's Japanese	MRA005JP	35	Multiple Doses: 8 mg/kg Q2W	163 (80-244)
HV, Japanese	MRA220JP	31	Single Dose: 8 mg/kg	137±22.7
Renal Impairment, Japanese	MRA221JP	8	Single Dose: 8 mg/kg in subjects with varying degrees of renal impairment:	
			normal	176
			mild	174± 29.1
			moderate	177± 18.9
			severe	172± 35.0
RA, Japanese	MRA009JP	162	Multiple Doses Q4W:	
			4 mg/kg	72.3 ± 16.1 to
			8 mg/kg	160 ± 36.5
RA, Japanese	LRO301	310 (PK)	Multiple Doses Q4W:	
			2 mg/kg	34.8± 11.4
			4 mg/kg	73.4± 17.6
			8 mg/kg	160± 42.9
RA	WA22762	629	Multiple Doses: 4 mg/kg Q4W, Week 24 exposure	**67.7± 17.7 (32.0−223)**
RA	WA22762	629	Multiple Doses: 8 mg/kg Q4W, Week 24 exposure	**153± 42.1 (64.1−492)**

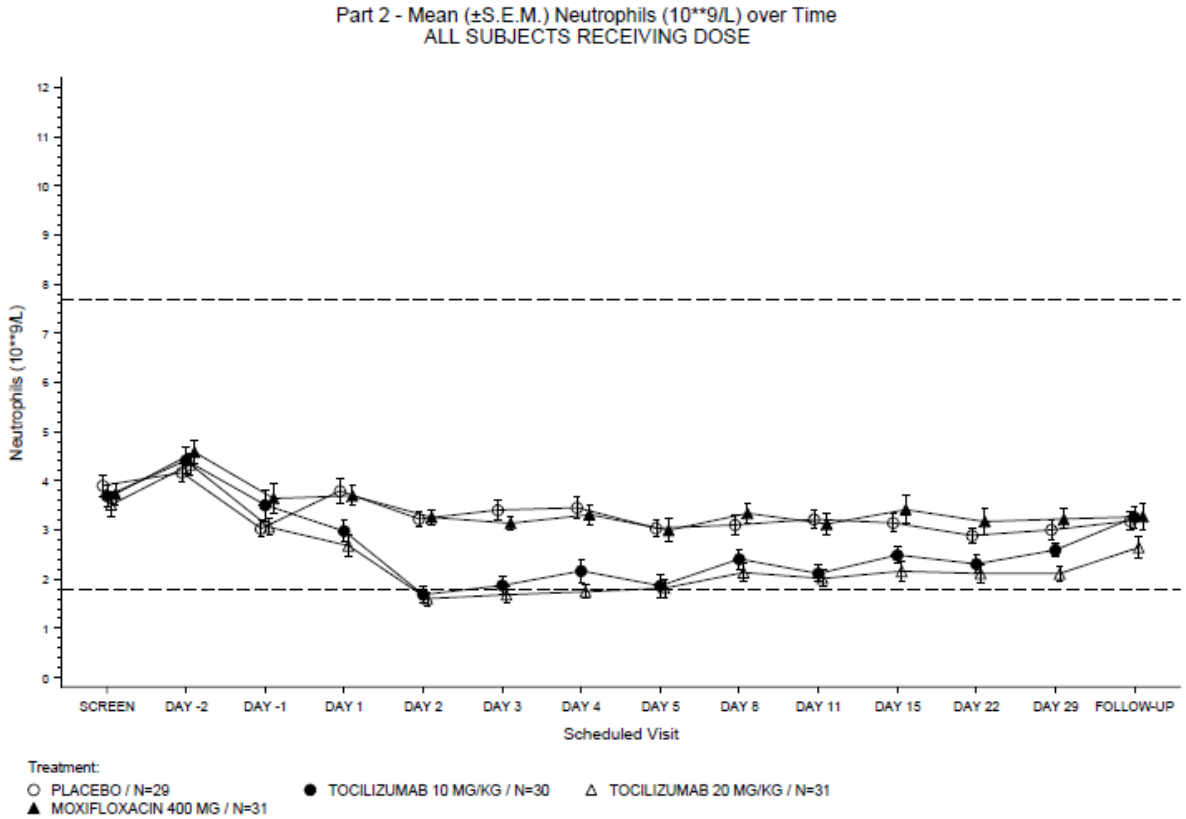
mean **±** SD (min-max) Normal font = observed; in **bold**, popPK model-predicted estimate due to sparse sampling employed in study design; after multiple doses exposure after last dose is provided unless specified otherwise

- Neutropenia: TQT study (Report 1028608).

The most common marked laboratory abnormality in the TQT study (BP19461) was low neutrophil counts (defined as an absolute value below 1.5 x 10^9/L and a decrease of 20% below baseline). In Part 1 of the study (Report 1025632), there was a dose-dependent increase in incidence of low neutrophil counts with 5/5 subjects with TCZ 28 mg/kg. Three of these five subjects had infection-related AEs of mild nasal congestion, mild mouth ulceration, mild vaginal candidiasis and mild herpes simplex. The remaining two subjects did not report infection-related AEs. In Part 2 (Report 1028608), the markedly low neutrophil counts were observed in 3/29 subjects in the placebo group,18/30 in the TCZ 10 mg/kg group, 23/31 subjects in the TCZ 20 mg/kg group and 2/31 in the moxifloxacin 400 mg group. Of the 46 subjects with markedly low neutrophil counts, 14 also had markedly low WBCs (defined as an absolute value below 3.0 x 10^9/L and a decrease of 30% below baseline). Decreases were observed in mean neutrophil counts following single doses of TCZ over the first 2 days post-treatment, reaching a maximum at approximately 24 hours after the infusion (i.e., Day 2). The mean minimum value for neutrophil counts (NTT_{min}) for subjects who received TCZ was similar: 1.42 x 10^9/L after 10 mg/kg and 1.31 x 10^9/L after 20 mg/kg; low neutrophil count recovered faster in subjects who received TCZ 10 mg/kg compared with subjects who received TCZ 20 mg/kg. There was no reduction in neutrophil count with placebo. The period of low neutrophil counts following either dose was not accompanied by an increase in immature neutrophils.

Although the observed incidence of marked decreases in neutrophil counts increased with the higher dose of tocilizumab (23/31 subjects in the tocilizumab 20 mg/kg group and 18/30 in the tocilizumab 10 mg/kg group), there did not appear to be a corresponding increase in the observed incidence of AEs, specifically the incidence of infections.

Figure 6: Absolute Neutrophil Values (Mean ± SEM) over Time (Safety Population, BP19461, Part 2)



Dashed horizontal lines in the figure indicate the upper and lover limits of the normal range

- Neutropenia: Population PK-PD based approach in a large RA patient database

A popPK-PD based approach (SCP for IV BLA) was taken to evaluate the correlation between TCZ levels and neutropenia (as an AE or lab abnormality) using pooled data from the two adult Phase III studies (WA17822 and WA18063) with a total of 16623 neutrophil values from 1702 RA patients based on mostly on IV doses of 4 and 8 mg/kg given every 4 weeks (Q4W). The model predictive performance was subsequently evaluated using internal and external validation, the latter with the data from study WA18062 (4285 neutrophil values from 444 patients).

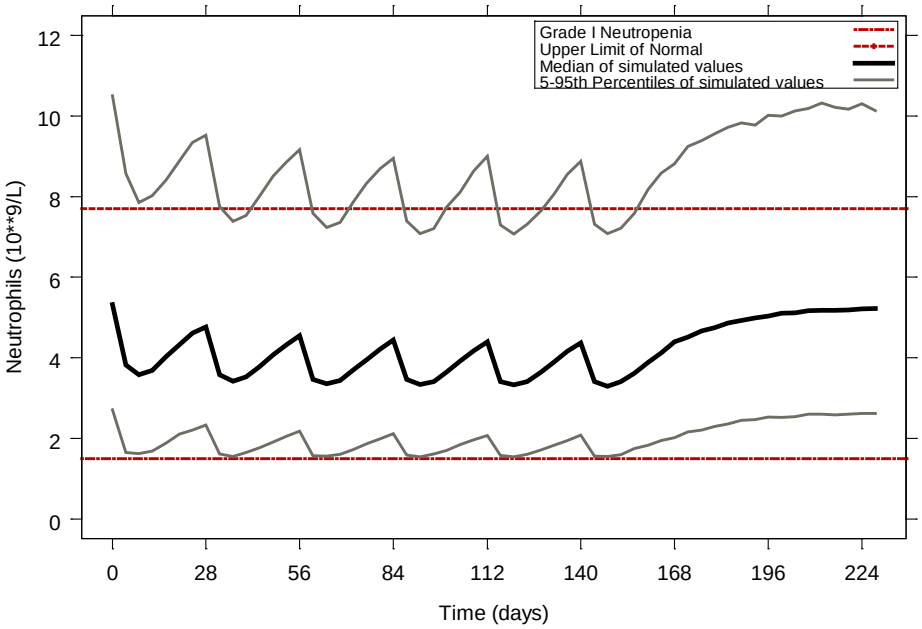
There was a clear exposure-response relationship for neutrophil count. Neutrophil count decreased with increasing exposure. The stimulation of the loss rate of neutrophils from the blood compartment by TCZ (K_{out}) was best described by a sigmoid E_{max} relationship in the indirect response model. The typical serum TCZ concentration at which 50% of the maximum effect (EC_{50}) is reached, was 7.42 µg/mL (between-patient variability of 79%). The maximum effect of TCZ on the stimulation of neutrophil loss from the blood compartment (E_{max}) was estimated at 0.792 (between-patient variability of 39%), translating into a mean maximum decrease of circulating neutrophils of 44%. The hill coefficient above unity (2.16) indicated a relatively steep relationship between exposure and circulating neutrophils.

Within a dosing interval, E_{max} is reached with concentrations for both 4 and 8 mg/kg. However, for 8 mg/kg, the concentrations stay at E_{max} for a longer period of time. This does not lead to a worsening of neutrophil decline but only to less fluctuation between infusions for this dose. Neutrophil time courses

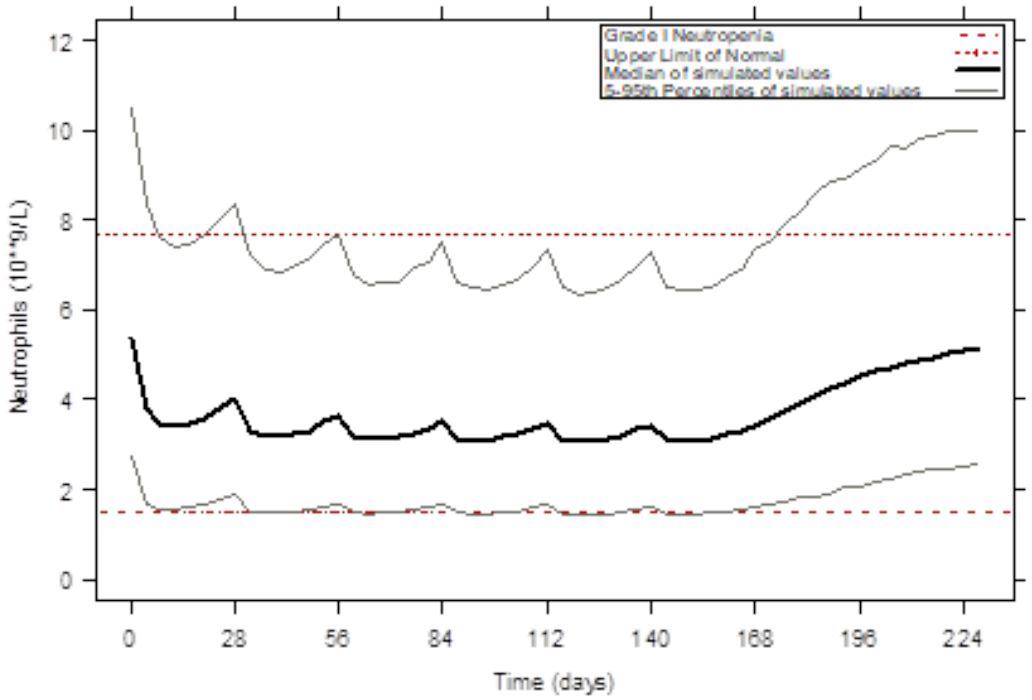
were simulated for the 4 and 8 mg/kg doses using the above model. At 8 mg/kg, fluctuations in neutrophil count were less pronounced than at 4 mg/kg as the TCZ effect on the neutrophil decrease was close to its maximum effect, suggesting that with higher TCZ exposures, neutrophil count reaches a plateau with no further decrease.

Figure 7: Predicted Median Time Course of Neutrophils and 90% Prediction Interval at (A) 4 and (B) 8 mg/kg Tocilizumab every 4 Weeks

(A)



(B)



The above model was also used to calculate the percentage of patients with Grade 1 to 4 AEs of neutropenia (Table 5). The exposure-dependent effect on neutrophil decreases did not result in an increased incidence of Grade 4 (< $0.5*10^9$/L) neutropenia. This is consistent with results observed in the Phase III studies.

Table 5: Simulated Percentage of Patients* with NCI-CTC Grades 1 to 4 of Neutropenia for 4 and 8 mg/kg TCZ

	4 mg/kg				8 mg/kg			
	Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
Grade 1 (< LLN and > $1.5*10^9$/L)	21.9	0.67	20.3	23.5	25.3	0.45	24.2	26.4
Grade 2 (< 1.5 and > $1*10^9$/L)	13.5	0.69	11.7	15.4	16.7	0.50	15.1	17.8
Grade 3 (< 1 and > $0.5*10^9$/L)	2.5	0.35	1.7	3.3	3.6	0.36	2.7	4.5
Grade 4 (< $0.5*10^9$/L)	0.027	0.042	0.00	0.17	0.049	0.046	0.00	0.20

*N = 108500; LLN lower limit of normal.

Paediatric patients

In paediatric patients, C_{max} has also been characterised. The highest model predicted concentrations are in the systemic juvenile idiopathic arthritis (sJIA) population with values ranging from 109-382 µg/ml (mean 245 µg/ml). TCZ administered to paediatric patients with sJIA induces a decline in circulating neutrophil counts. PopPK-PD model was used to describe the relationship between TCZ concentrations

and the time course of neutrophil decline. EC_{50} value was 6.38 µg/mL (%RSE 15.8%), a value very similar to EC_{50} of 7.49 µg/mL (%RSE 2.2%) estimated for the adult patients. The E_{max} value of 0.724 (%RSE 14.8%) was also similar to E_{max} of 0.788 (%RSE 2.4%) in adult patients.

Table 6: List of primary IV TCZ studies and associated C_{max} in paediatrics with PK endpoints

Disease population	**Study number**	**N**	**Dose / Duration**	***C_{max} (µg / ml)**
sJIA	WA18221	n =75, PK pop	8 mg/kg in patients ≥ 30 kg; 12 mg/kg in patients < 30 kg, or placebo Q2W × 6 (double-blind phase) followed by 8 mg/kg in patients ≥ 30 kg or 12 mg/kg in patients < 30 kg Q2W (open phase); week 12 exposures Duration: until commercial availability	**245 ± 57.2 (109 – 382)**
sJIA	NP25737	11	12 mg/kg Q2W Duration: 12 weeks (with optional extension period: until patients have reached 2 years of age or have been treated for 1 year from baseline)	**288 ± 40.4 (195 – 347)**
pJIA	WA19977	n =177, PK pop	8 mg/kg in patients ≥ 30 kg; 8 or 10 mg/kg in patients < 30 kg Q4W × 4 (open phase) followed by 8 mg/kg in patients ≥ 30 kg, 8 or 10 mg/kg in patients < 30 kg, or placebo Q4W × 6 (double-blind withdrawal phase) followed by TCZ: 8 mg/kg in patients ≥ 30 kg; 8 or 10 mg/kg in patients < 30 kg Q4W until Week 104 (open phase); week 16 exposure Duration: Until commercial availability	**173 ± 37.8 (91.6 – 341)**

mean ±SD (min-max) reported. Normal font = observed; in **bold**, popPK model-predicted estimate due to sparse sampling employed C_{max} is a popPK model-predicted estimate

Exposure-safety analysis

Study WA18221 was a phase III study investigating the efficacy and safety of TCZ in the treatment of sJIA using the same TCZ IV doses proposed for CRS (i.e. 12 mg/kg for patients < 30 kg, 8 mg/kg for patients ≥ 30 kg) but given in a chronic use setting every 2 weeks for up to 5 years. The study comprised an initial randomised, double-blind, placebo controlled period of 12 weeks duration, followed by an open-label extension where all patients received IV TCZ. This response focuses on the results obtained in the study up to Week 12 (included in variation EMEA/H/C/000955/II/015).

The safety profile in study WA18221 was consistent with the well-established safety profile of TCZ. The majority of AEs were mild to moderate in intensity, reversible, and not treatment-limiting, and were mostly infections, driven by upper respiratory infections, nasopharyngitis and gastroenteritis. There were few SAEs, no deaths, and no withdrawals due to laboratory abnormalities. There were no sustained significant laboratory changes from baseline, including in lipids, liver enzymes, renal function, haemoglobin, white blood cell count, and platelets.

The incidence of infections was higher in the < 30 kg body weight group who received 12 mg/kg IV TCZ Q2W compared to the ≥ 30 kg group who received 8 mg/kg IV TCZ Q2W. However, several factors could have contributed to this finding. Patients weighing < 30 kg were younger, and upper respiratory infections are seen frequently and are typical in young children. In addition, a higher proportion of patients weighing < 30 kg were receiving concomitant MTX and corticosteroids at baseline compared to the ≥ 30 kg group (MTX 81.6% vs 56.8%, and CS ≥ 0.3 mg/kg/d; 74% vs 24%, respectively).

The results of exposure-safety analyses were consistent with those obtained in the adult RA clinical trial program. A summary of percentages of patients reporting AEs and SAEs by body system and preferred term to Week 12 was performed by AUC_{2weeks}, C_{max} and C_{min} exposure quartiles. When comparing AEs across AUC_{2weeks} exposure quartiles, there was no trend towards an increased incidence in the percentage of patients reporting at least one AE with increasing TCZ exposure in the infections and infestations, gastrointestinal disorders, skin and subcutaneous tissue disorders, nervous system disorders, or respiratory, thoracic, and mediastinal disorders system organ classes. Other AEs occurred at a low incidence across exposure quartiles. When comparing SAEs across AUC_{2weeks} exposure quartiles, most SAEs occurred in patients in the first exposure quartile (Q1) and, therefore, there was no trend toward an increased incidence in percentage of patients with SAEs with increasing TCZ exposure.

Table 7: Summary of Percentage of patients Reporting AEs by Body System and Preferred Term to Week 12 of Study WA18221 by AUC_{2weeks}, C_{max} and C_{min} Exposure Quartiles

Body System/Adverse Event*	AUC_{2weeks}			
	Q1 N=19 No. (%)	Q2 N=19 No. (%)	Q3 (N=19) No. (%)	Q4 N=18 No. (%)
All Body Systems	19 (100)	16 (84.2)	17 (89.5)	14 (77.8)
Infections and Infestation	11 (57.9)	8 (42.1)	6 (31.5)	9 (50)
Gastrointestinal disorders	3 (15.8)	5 (26.3)	2 (10.5)	4 (22.2)
Skin and Subcutaneous Tissue disorders	4 (21.1)	1 (5.3)	3 (15.8)	4 (22.2)
Nervous System disorders	3 (15.8)	1 (5.3)	2 (10.5)	2 (11.1)
Respiratory, Thoracic, and Mediastinal disorders	3 (15.8)	1 (5.3)	2 (10.5)	1 (5.6)
	C_{max}			
	Q1	Q2	Q3	Q4
All Body Systems	18 (94.7)	16 (84.2)	18(94.7)	14 (77.8)
Infections and Infestation	9 (47.4)	6 (31.6)	10 (52.6)	9 (50)
Gastrointestinal disorders	2 (10.5)	2 (10.5)	8 (42.1)	2 (11.1)
Skin and Subcutaneous Tissue disorders	4 (21.1)	2 (10.5)	2 (10.5)	4 (22.2)
Nervous System disorders	2 (10.5)	2 (10.5)	3 (15.8)	1 (5.6)
Respiratory, Thoracic, and Mediastinal disorders	2 (10.5)	2 (10.5)	2 (10.5)	1 (5.6)
	C_{min}			
	Q1	Q2	Q3	Q4
All Body Systems	19 (100)	16 (84.2)	16 (84.2)	15 (83.3)
Infections and Infestation	10 (52.6)	9 (47.4)	6 (31.6)	9 (50.0)
Gastrointestinal disorders	2 (10.5)	5 (26.3)	3 (15.8)	4 (22.2)
Skin and Subcutaneous Tissue disorders	3 (15.8)	2 (10.5)	3 (15.8)	4 (22.2)
Nervous System disorders	2 (10.5)	2 (10.5)	2 (10.5)	2 (11.1)
Respiratory, Thoracic, and Mediastinal disorders	3 (15.8)	1 (5.3)	2 (10.5)	1 (5.6)

* Total patients with at least one AE; Only most frequent AEs were summary in this table. Full listings can be found in the source data.

Table 8: Summary of Percentage of patients Reporting SAEs by Body System and Preferred Term to Week 12 of Study WA18221 by AUC_{2weeks}, C_{max} and C_{min} Exposure Quartiles

Body System/SAE*	AUC_{2weeks}			
	Q1 N=19 No. (%)	Q2 N=19 No. (%)	Q3 (N=19) No. (%)	Q4 N=18 No. (%)
All Body Systems	3 (15.8)	-	-	-
Infections and Infestation	2 (10.5)	-	-	-
Skin and Subcutaneous Tissue disorders	1 (5.3)	-	-	-
	C_{max}			
	Q1	Q2	Q3	Q4
All Body Systems	2 (10.5)	-	1 (5.3)	-
Infections and Infestation	2 (10.5)	-	-	-
Skin and Subcutaneous Tissue disorders	-	-	1 (5.3)	-
	C_{min}			
	Q1	Q2	Q3	Q4
All Body Systems	3 (15.8)	-	-	-
Infections and Infestation	2 (10.5)	-	-	-
Skin and Subcutaneous Tissue disorders	1 (5.3)	-	-	-

* Total patients with at least one SAE;

An analysis of low neutrophil counts by PK exposure quartiles (AUC_{2weeks}, C_{min}, C_{max}) showed a trend towards more severe neutropenia with higher TCZ exposures, as mean exposures (AUC_{2weeks}, C_{min}, C_{max})

were similar between patients with grade 0 (n=59) and grade 2 low neutrophil counts (n=10), whereas patients with CTC grade 3 events (n=5) had higher TCZ exposures (Table 9). These findings were consistent with those observed in adult RA.

Table 9: Summary of TCZ PK Exposures by Worst Neutrophil CTC Grades at Week 12 in Study WA18221 for All Patients

Parameter		Grade 0 N=59	Grade 1 N=0	Grade 2 N=10	Grade 3 N=5	Grade 4 N=0
C_{max}, µg/mL	Mean ±SD	243 ±62.7	-	252 ±32.8	257 ±24.8	-
	CV%	25.8	-	12.0	9.6	-
C_{min}, µg/mL	Mean ±SD	56.2 ±24.6	-	57.0 ±14.5	75.8 ±20.2	-
	CV%	43.8	-	25.4	26.6	-
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD	1313 ±435	-	1357 ±304	1672 ±272	-
	CV%	33.1	-	22.4	16.3	-

2.3.3. Pharmacodynamics

Mechanism of action

Emerging evidence suggests that IL-6 is the cytokine that is the central mediator of toxicity in CRS. IL-6 is produced by a wide variety of cell types, including T-cells, B-cells, monocytes, macrophages, fibroblasts, dendritic and endothelial cells. IL-6 also acts on a wide variety of cell types and is involved in T-cell differentiation and activation, B-cell maturation, neutrophil trafficking.

CRS is associated with high IL-6 levels (Panelli et al. 2004; Doessegger and Longauer Banholzer, 2015; Lee et al. 2014a). For patients treated with CD19 CAR T-cell therapy, IL-6 may correlate with the severity of CRS, with patients who experience severe or life-threatening CRS (CTCAE Grades 4 or 5) having much higher IL-6 levels compared to their counterparts who do not experience CRS or who experience milder CRS reactions (CTCAE Grades 0-3; Chen et al. 2016). IL-6 levels during a CRS episode are highly elevated, to the ng/mL range, which given the known biology of IL-6 would cause significant IL-6 trans-signalling and a marked inflammatory response.

2.3.4. PK/PD modelling

Although the plasma levels of tocilizumab in the approved indications and dose regiments is much lower, e.g. pJIA and sJIA (see tables below), the maximum observed C_{max} was 649 µg/mL in five healthy subjects after a single dose of 28 mg/kg tocilizumab during a study to evaluate of the safety of supratherapeutic doses following single doses in healthy subjects. Tocilizumab doses of 2, 10, 20 and 28 mg/kg were administered as an intravenous infusion over a 1 hour period. The highest systemic exposures to tocilizumab were achieved with the 28 mg/kg dose, with mean AUC_{inf} and C_{max} values of 147000 h*µg/mL and 558 µg/mL, respectively. Mean CL was estimated as 0.609 mL/h/kg for the 2 mg/kg dose and decreased with increasing doses to 0.192 mL/h/kg for the highest dose of 28 mg/kg. Mean t1/2 ranged from 54 hours after 2 mg/kg to 293 hours after 28 mg/kg. Mean V_{ss} ranged from 50.0 (2 mg/kg) to 85.7 mL/kg (20 mg/kg). Median t_{max} was between 3 and 4 hours for all doses investigated.

Single doses of 2, 10, 20 and 28 mg/kg of tocilizumab were well tolerated. No unexpected safety findings were observed. Of note is that although the 28 mg/kg dose was associated with no immediate safety issues, the potential implications of decreases in neutrophils over a prolonged period of time with this dose, precluded its selection for part 2 of the study. The 20 mg/kg dose was considered the highest safe

and tolerable dose to be administered to a large group of healthy volunteers in the thorough QT part of this study. This dose resulted in mean C_{max} of 410 µg/mL.

Table 10 estimated PK parameters for tocilizumab in pJIA.

Dosing Regimen	n	Body Weight (kg) median min–max	C_{min} (µg/mL) mean±SD median (min–max)	C_{max} (µg/mL) mean ± SD median (min–max)	$AUC_{12weeks}$ (µg/mL • day) mean ± SD median (min–max)	C_{mean} (µg/mL) mean±SD median (min–max)
TCZ SC in pJIA						
162 mg SC Q3W BW <30 kg	27	20.0 12.0–28.0	18.38±12.87 13.35 (0.21–52.25)	75.46 ± 24.1 62.44 (39.37–121.13)	3826±1164 2998 (1465–7708)	45.54 ± 19.81 35.69 (17.44–91.76)
162 mg SC Q2W BW ≥30 kg	25	54.7 34.2–97.9	11.79±7.08 12.71 (0.19–23.75)	29.37±13.54 29.74 (7.56–50.3)	1821±873 1933 (324–3098)	21.68 ± 10.39 23.01 (3.86–36.89)
TCZ IV in pJIA						
10 mg/kg IV Q4W BW <30 kg	35	20.9 9.6–29.5	1.47±2.44 0.35 (0–11.81)	168.37±24.84 166.61 (125.44–219.64)	2656±658 2586 (1341–4035)	31.61 ± 7.84 30.79 (15.96–48.04)
8 mg/kg IV Q4W BW ≥30 kg	119	48.4 30.7–85.1	6.55±7.93 3.28 (0.02–35.4)	182.96±42.32 181.15 (114.46–330.52)	3543±1126 3244 (1862–7038)	42.18 ± 13.4 38.62 (22.16–83.79)

Note: The corresponding SC and IV BW treatment regimens from Study WA28117 and Study WA19977 are highlighted with matching colors.

AUC=area under the concentration-time curve; BW=body weight; C_{max}=maximum concentration; C_{min}=minimum concentration; IV=intravenous; Q2(3)(4)W=every 2(3)(4) weeks; SC=subcutaneous; SD=standard deviation.

Table 11: estimated PK parameters for tocilizumab in sJIA.

Dosing Regimen	Weight Group	n	Median BW (Min – Max) (kg)	C_{min} (µg/mL) Mean ± SD Median (Min – Max)	C_{max} (µg/mL) Mean ± SD Median (Min – Max)	$AUC_{0-2weeks}$ (µg/mL×day) Mean ± SD Median (Min – Max)
TCZ SC in sJIA						
162 mg SC Q2W	BW < 30 kg	25	19.6 9.2 – 27.2	65.86 ± 31.31 64.15 (16.61 – 135.86)	134.1 ± 58.64 126.6 (51.67 – 265.84)	1414 ± 605 1298 (539 – 2792)
162 mg SC QW	BW ≥ 30 kg	26	51.7 30.0 – 73.2	79.18 ± 35.57 72.37 (19.52 – 157.81)	99.75 ± 46.19 89.8 (26.37 – 190.2)	1278 ± 565 1154 (334 – 2370)
TCZ IV in sJIA						
12 mg/kg IV Q2W	BW < 30 kg	46	18.9 10.0 – 29.7	68.4 ± 29.97 65.86 (18.99 – 135.48)	273.8 ± 63.8 274.4 (148.8 – 443.96)	1721 ± 505 1734 (840 – 2712)
8 mg/kg IV Q2W	BW ≥ 30 kg	43	42.3 30.6 – 112.7	69.74 ± 29.1 70.73 (5.26 – 126.62)	255.8 ± 60.77 253.0 (119.58 – 404.34)	1662 ± 504 1631 (526 –2779)

Note: The corresponding SC and IV BW treatment regimens from Study WA28118 and Study WA18221 are highlighted with matching colors.

The number of TCZ IV sJIA patients includes all patients randomized to TCZ in Part I of the study as well as any patient who escaped from placebo to TCZ in Part I and had a PK sample available.

AUC=area under the concentration-time curve; BW=body weight; C_{max}=maximum concentration; C_{min}=minimum concentration; IV=intravenous; QW=every week; Q2W=every 2 weeks; SC=subcutaneous; SD=standard deviation.

Sources for BWs: t_dm_SE (WA28118) and 12-Week WA18221 CSR, Table 7.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics (PK) data from the CAR T-cell trials were available for 27 patients after the first dose of TCZ and for 8 patients after a second dose of TCZ. The PK population included 15 male and 12 female patients of median age 12 years (range, 4-23 years). The geometric mean (% CV) maximum concentration of TCZ in the patients with CAR T-cell-induced, severe or life-threatening CRS was 99.5 µg/mL (36.8%) after the first infusion and 160.7 µg/mL (113.8%) after the second infusion. The population PK model developed in paediatric 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 (VC) of 1.8 L (RSE = 11.2%) using PK data from patients with CRS. 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. 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 µg/mL and no trend was observed towards increased incidence in AEs or SAEs with increasing tocilizumab exposure in 122 patients. 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.

The scientific rationale for the mechanism of action, i.e. blocking the pro-inflammatory action of IL-6 using the anti-IL-6R antibody is already established.

Overall, it is expected that C_{max} of tocilizumab after administration of 2 doses separated by at least 8 hours would be comparable to the concentrations reached in other approved indications (e.g. pJIA, sJIA; see tables above). An exposure- safety analysis is presented to resolve any uncertainty about the tocilizumab exposure that might be reached after up to 4 doses; these data revealed no significant clinical findings (see discussion on clinical safety).

According to PK modelling conducted, the estimated median C_{max} in patients with CRS treated with 4 doses tocilizumab separated by 8 hours is 312 µg/mL (2.5th, 97.5th percentiles: 151 µg/mL, 606 µg/mL) and therefore higher than the exposure of the presently approved posology. PK data from subjects that have been exposed to comparable tocilizumab concentrations (up to the maximum estimated C_{max} of 606 µg/mL) in the overall tocilizumab clinical development program were provided; a summary of IV TCZ studies and associated C_{max} in adults and paediatrics was presented. Comparable maximum TCZ concentrations that are expected to be reached after 4 doses separated by 8 hours (312 µg/mL; 151 µg/mL - 606 µg/mL) have solely been observed in 5 healthy adult subjects treated with 28 mg/kg TCZ in study BP19461.

In paediatrics, the highest C_{max} were observed in the sJIA study WA18221 (245 ± 57.2 µg/mL). The intended posology in CRS is expected to lead to significantly higher exposure in paediatrics. A comparison of AEs across AUC_{2weeks} exposure quartiles in Study WA18221 revealed no trend towards an increased incidence in the percentage of patients reporting at least one AE with increasing TCZ exposure. When comparing SAEs across AUC_{2weeks} exposure quartiles most SAEs occurred in the first exposure quartile indicating that there was no trend towards an increased incidence in percentage of patients with SAEs with increasing TCZ exposure.

Independent of age (adults vs. paediatrics), a relationship between higher TCZ exposure and lower neutrophil count, is well studied however there was no correlation to any increase in the incidence of AEs, particularly infections (see discussion on Clinical Safety), therefore the CHMP did not raise any concern.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data available are sufficient to support the role of RoActemra in CRS related to CAR-T therapy and the recommended posology.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response study was conducted.

The intended posology of tocilizumab in treatment of CAR T cell induced CRS is 8 mg/kg IV for subjects weighing ≥ 30 kg and 12 mg/kg IV for subjects weighing less than 30 kg, which corresponds to the IV dosing regimen in sJIA patients. Depending on the response, up to 4 doses of tocilizumab may be administered, separated by at least 8 hours.

Table 1 below describes the already EU-approved dosage forms and regimens for tocilizumab.

Table 1 Approved Tocilizumab Dosage Forms and Regimens for Adults (RA and GCA) and Children (pJIA, sJIA) in the EU

Dosage Form, Routes of Administration	Solution for injection • Single-use vials for IV (at strength of 20 mg/mL), as 80 mg per 4 mL, 200 mg per 10 mL, and 400 mg per 20 mL. Infused over a period of 1 h. • Single-use prefilled syringe for SC of 162 mg (at strength of 180 mg/mL) in 0.9 mL.		
Dosing Regimen	RA	Adult patients	IV 8 mg/kg q4w, with adjustment to IV 4 mg/kg q4w in case of laboratory abnormalities [a]
		Adult patients	SC 162 mg q1w
	GCA	Adult patients	SC 162 mg q1w
	pJIA	Patients < 30 kg	IV 10 mg/kg q4w SC 162 mg q3w
		Patients ≥ 30 kg	IV 8 mg/kg q4w SC 162 mg q2w
	sJIA	Patients < 30 kg	IV 12 mg/kg q2w
		Patients ≥ 30 kg	IV 8 mg/kg q2w

GCA: giant cell arteritis; IV: intravenous; qxw: once every *x* weeks; pJIA: polyarticular juvenile idiopathic arthritis; RA: rheumatoid arthritis; SC: subcutaneous; sJIA: systemic juvenile idiopathic arthritis.

a Doses exceeding 800 mg per infusion are not recommended in RA patients.

2.4.2. Main studies - *Published retrospective analysis (Le et al, 2018)*

This is a retrospective analysis of TCZ/CRS data from the CAR T-cell trials (Le et al. 2018).

Methods

The clinical trials included 5 studies of CTL019 (A2201, B2101J, B2102J, B2202, B2205J) and 4 studies of KTE-C19 (101, 102, 103 and 104).

Study participants

The patient population was restricted to patients with Grade 3 or 4 CRS and who had been treated using intravenous tocilizumab 8 mg/kg (12 mg/kg for patients <30 kg); this is the recommended dose approved for systemic juvenile idiopathic arthritis (SJIA).

Treatments

Treatment with tocilizumab was pre-specified in each protocol, but the exact dose, frequency and criteria for treatment varied. The efficacy-evaluable population was limited to patients who had been treated using intravenous tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg).

Objectives

The primary objective was to characterise resolution of CRS which was defined as the patient having absence of fever and being off vasopressors for at least 24h.

Outcomes/endpoints

Patients were considered responders if CRS resolved within 14 days of the first dose of TCZ, if no more than 2 doses of TCZ were needed, and if no drugs other than TCZ and corticosteroids were used for treatment.

Response after 2, 7, and 21 days was also assessed.

The majority of patients who achieved a response did so within the first 7 days (n = 8, 53.3%).

Sample size

This was a retrospective analysis; no sample size calculations were performed.

Randomisation

N/A

Blinding (masking)

N/A

Statistical methods

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

Results

Baseline data

Table 12: Demographics in the retrospective analysis Le et al 2018

Demographics	CTL019 N= 45 n (%)	KTE C19 N=15 n (%)
Median age (range) years,	12 (3-23)	60 (9-75)

Demographics	CTL019 N= 45 n (%)	KTE C19 N=15 n (%)
Age category		
2 to <12	20 (44.5)	1 (6.7)
12 to < 18	15 (33.3)	0
≥18	10 (22.2)	14 (93.3)
Sex		
Male	24 (53.3)	10 (66.7)
Female	21 (46.7)	5 (33.3)
Race		
White	37 (82.2)	13 (86.7)
Asian	1 (2.2)	0
Other	7 (15.6)	2 (13.3)
Ethnicity		
Hispanic or latino	7 (15.6)	4 (26.7)
Other	38 (84.4)	11 (73.3)
Underlying malignancy		
ALL	45 (100)	2 (13.3)
DLBCL	0	12 (80.0)
PMBCL	0	1 (6.7)

Numbers analysed

The patient population was restricted to patients with Grade 3 or 4 CRS and who had been treated using intravenous tocilizumab 8 mg/kg (12 mg/kg for patients <30 kg); this is the recommended dose approved for systemic juvenile idiopathic arthritis (SJIA).

Of the 58 patients in CTL019 series treated with tocilizumab 45 subjects fulfilled these criteria.

Of the 76 patients treated with tocilizumab in KTE-C19 studies only 15 subjects fulfilled criteria.

Outcomes and estimation

Eight patients (53%) with ALL, DLBCL or PMBCL from the KTE-C19 studies achieved a response within 14 days of the first dose of TCZ, and the median time from the first dose of TCZ to response was 4.5 days (range, 2–7 days). The response rates were reported to be largely consistent among subgroups such as age group, sex, race, ethnicity, grade of CRS at first dose of TCZ, and duration of CRS prior to treatment with TCZ.

Thirty-one patients (69%) with ALL from the CTL-019 series achieved a response within 14 days of the first dose of TCZ, and the median time from the first dose of TCZ to response was 4 days (range, 1-12 days). The response rates were reported to be largely consistent among subgroups such as age group, sex, race, ethnicity, grade of CRS at first dose of TCZ, and duration of CRS prior to treatment with TCZ.

Response after 2, 7, and 21 days was also assessed. The majority of patients who achieved a response did so within the first 7 days (n = 26, 57.8%).

Table 13: Resolution of CRS in the efficacy populations

Analyses	CTL019 series ($n = 45$) responders *n* (%, 95% CI)	KTE-C19 series ($n = 15$) responders *n* (%, 95% CI)
Primary analysis:		
Response by day 14	31 (68.9, 53.4–81.8)	8 (53.3, 26.6–78.7)
Additional analyses		
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 21	31 (68.9, 53.4–81.8)	8 (53.3, 26.6–78.7)

Abbreviation: CI, confidence interval.

2.4.3 Data from clinical trials with CAR-T products

2.4.3.1. Kymriah (Tisagenlecleucel) - Clinical data evaluation with focus on CRS

Data from tisagenlecleucel studies in Diffuse large cell lymphoma (DLBCL) and Acute Lymphocytic leukaemia (ALL) are reviewed.

Table 14: Summary of anti-cytokine therapy during CRS in patients who required at least one dose of tocilizumab in Novartis Studies B2202, B2205J and C2201 (Safety set – Patients with CRS)

	Study B2202 N=58	**Study B2205J N=26**	**Study C2201 N=64**	***All patients N=148***
Systemic anti-cytokine therapy given - n (%)	28 (48.3)	7 (26.9)	17 (26.6)	*52 (35.1)*
Tocilizumab	28 (48.3)	7 (26.9)	16 (25.0)	*51 (34.5)*
1 dose	17 (29.3)	2 (7.7)	6 (9.4)	*25 (16.9)*
2 doses	8 (13.8)	2 (7.7)	10 (15.6)	*20 (13.5)*
3 doses	3 (5.2)	3 (11.5)	0	*6 (4.1)*
Siltuximab	5 (8.6)	0	0	*5 (3.4)*
Corticosteroids	14 (24.1)	5 (19.2)	12 (18.8)	*31 (20.9)*
Other	2 (3.4)	5 (19.2)	0	*7 (4.7)*

- Data cut-offs: B2202: 25-Apr-2017; B2205J: 1-Feb-2016; C2201: 8-Dec-2017

Diffuse large B-cell lymphoma– Study C2201

The application for the DLBCL indication is primarily based on one phase II, open-label, single arm trial in adult patients with r/r DLBCL (after ≥ 2 lines of chemotherapy and not eligible for SCT) (C2201/Juliet). All patients had to have a life expectancy ≥ 12 weeks, ECOG PS 0-1 and adequate organ function.

The clinical development program of tisagenlecleucel includes one Phase II, multi-centre, single-arm study to evaluate the clinical efficacy, safety and cellular kinetics of tisagenlecleucel in the target population of r/r DLBCL.

Table 15: Overview of study C2201

Study No of patients	Study design Date of DBL	Study endpoints	Study status
[Study C2201] N=99 (n=81 in the Main Cohort)	A Phase II, multicenter, single-arm, open-label study in adult patients with r/r DLBCL 08-Jun-2017	*Primary:* ORR by IRC *Secondary:* DOR, EFS, PFS, TTR by IRC, and OS	Ongoing

DBL = database lock; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS = event-free survival; IRC = Independent Review Committee; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; r/r = relapsed or refractory; TTR = time to response

Data from CTL019 treated patients experiencing CRS show marked elevations in IL-6, IFN-g, and less intensely TNF. The symptoms occur in 1-14 days after cell infusion and may include high fevers, rigors, myalgia/arthralgia, nausea/vomiting/anorexia, fatigue, headache, encephalopathy, hypotension, dyspnoea, tachypnoea and hypoxia. Supportive care and tocilizumab have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most patients; however, several patients with a suboptimal response to the first dose of tocilizumab have received a second dose of tocilizumab (within 3-5 days) with CRS resolution.

A detailed treatment algorithm has been established with clear criteria for CRS management and guidance on when to administer tocilizumab. This approach was designed to avoid life-threatening toxicities, while attempting to allow the CTL019 transduced cells to establish a proliferative phase which appears to correlate with tumour response.

A modification of the Common Terminology Criteria for Adverse Events (CTCAE) CRS grading scale has also been established to better reflect CTL019-therapy-associated CRS.

Table 16: CAR-T therapy associated grading for CRS; The Penn Grading Scale for CRS (PGS-CRS)

- Marked elevations in IL-6, interferon gamma and less intensely TNF
- Symptoms occur 1 to 14 days after cell infusion
- Symptoms may include: high fever, rigors, myalgia, arthralgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea and hypoxia

1	2	3	4
Mild reaction: Treated with supportive care such as antipyretics and antiemetics.	Moderate reaction: Requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests [LFTs]) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids or low dose vasopressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	Life-threatening complications such as hypotension requiring high dose vasopressors (see Table 6-2) or hypoxia requiring mechanical ventilation.

Adverse events of CRS

58% of patients with DLBCL experienced an AE of CRS. One patient (1.0%) was reported with histiocytosis hematophagy in addition to CRS. SAEs of CRS were reported in 29 patients (29.3%), and grade 3/4 events were reported in 23 patients (23.2%). There were no deaths due to CRS. CRS was graded according to the modified Penn grading system (Porter et al 2015), which is more conservative than the Lee grading scale (Lee et al 2014).

Events of CRS (n=57) were reported over a range of severities in the majority of patients treated with tisagenlecleucel and CRS was the most frequent SAE associated with tisagenlecleucel therapy.

Table 17: CRS post – Kymriah infusion period (Safety set)

CRS - n (%)	All patients N=99
No	42 (42.4)
Yes	57 (57.6)
Fatal – n (%)	0
Maximum CRS grade – n (%)	
Grade 1	11 (11.1)
Grade 2	23 (23.2)
Grade 3	15 (15.2)
Grade 4	8 (8.1)
Admitted to ICU - n (%) [1]	25 (43.9)
Duration of ICU stay (days)	
n	25
Mean (SD)	8.8 (8.11)
Median	6.0
Min - Max	2 - 34
Oxygen supplementation given - n (%)	24 (42.1)
Patient intubated - n (%)	8 (14.0)
Duration (days)	
n	8
Mean (SD)	7.9 (5.59)
Median	7.0
Min - Max	2 - 18
Patient dialyzed - n (%)	4 (7.0)
Duration (days)	
n	4
Mean (SD)	24.8 (22.54)
Median	25.0
Min - Max	2 - 47
Total Parenteral Nutrition used - n (%)	5 (8.8)
Duration (days)	
n	5
Mean (SD)	6.8 (7.46)
Median	2.0
Min - Max	2 - 19
Bleeding observed - n (%)	4 (7.0)
Blood product support given for bleeding - n (%)	3 (5.3)

Management of CRS

Patients were treated up to the highest dose of 6.0×108 CAR+ viable T cells. CRS was generally manageable with supportive care and anti-IL6 cytokine directed therapy. Of the 57 patients with CRS:

- 43.9% were admitted to the ICU (within a median time to admission of 5 days) as a consequence of CRS, where they stayed for median (maximum) duration of 6 days (34 days).
- 42.1% required oxygen supplementation, and 14.0% needed mechanical ventilation. Four patients (7.0%) required renal dialysis, and parenteral nutrition during CRS was required by 5 patients (8.8%).
- 28.1% received systemic anti-cytokine therapy. Tocilizumab was administered in 26.3% patients. Eight of these patients had grade 4, 6 had grade 3, and one patient had grade 1/2 CRS.
- Infections concurrent with CRS were reported in 12.3% patients.

Four patients (7.0%) required ICU admission due to CRS-related infections (lung infection, facial wound, GI infection (clostridium difficile) and infection in multiple sites (catheter tip, blood, GI, urine)).

Anti-IL-6 based therapies such as tocilizumab were administered for moderate or severe CRS associated with tisagenlecleucel. Tocilizumab was administered at doses that have been shown to be pharmacodynamically active and safe in approved indications.

Systemic anti-cytokine therapy was given to 16 of the 57 patients (28.1%) who presented with CRS. Consistent with the protocol-defined management of CRS, 15 of the 16 patients treated with anti-cytokine therapy (26.3% of patients with CRS) received tocilizumab treatment (1 dose in 6 patients, 2 doses in 9 patients). Corticosteroids were used in 19.3% of patients with CRS.

Among the 15 patients who received tocilizumab, 6 patients presented with CRS of grade 3 severity and 8 patients with grade 4 CRS

Table 18: Anti-cytokine therapy during CRS (Safety set – patients with CRS)

	All patients N=57
Systemic anti-cytokine therapy given - n (%)	16 (28.1)
Tocilizumab	15 (26.3)
1 dose	6 (10.5)
2 doses	9 (15.8)
Corticosteroids	11 (19.3)
Source: [Study C2201-Table 14.3.1-4.1]	

Relapsed/Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)- study B2202

Main clinical data came from the registration Study CTL019 B2202, a single arm, open-label, multicentre Phase 2 study. Serious and life-threatening AEs, in particular CRS, have been observed in most patients, in particular first eight weeks post-Kymriah infusion.

Table 19: Studies contributing to the safety evaluation of paediatric r/r ALL.

Novartis Study Code (Penn Study Code, if applicable)	Indication	CMC Process	Study Title	Source of safety listings
Pediatric ALL treatment protocols				
CTL019B2202 N³=75	Pediatric ALL	Novartis	A Phase II, single arm, multi-center study to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia	Interim CSR 2017 ARGUS
CTL019B2205J N³=29	Pediatric ALL	Penn (for first 29 patients), Novartis (for future patients)	A Phase II, single arm, multi-center study to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia	Interim CSR ARGUS
CTL019B2101J (CHP959) N³=56 (Non-CNS3 ALL patients)	Pediatric ALL	Penn	A phase I/IIa study of redirected autologous T cells engineered to contain anti-CD19 attached to TCRζ and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma	Interim CSR 2017 ARGUS
CTL019B2208J (16CT022)	Pediatric ALL	Penn	A Phase II, two cohort study of the tocilizumab optimization timing for CART19 (CTL019) associated cytokine release syndrome (CRS) management in pediatric patients with CD19 expressing relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)	ARGUS
CTL019B2001X	Pediatric and young adults ALL	Novartis	Expanded treatment protocol for relapsed/refractory pediatric/young adult acute lymphoblastic leukemia patients to be treated with CTL019	ARGUS
Other indication treatment protocols				
CTL019C2201 N³=99	Adult DLBCL	Novartis	A phase II, single arm, multi-center study to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	Interim CSR ARGUS
CTL019B2203J (UPCC21413)	Adult ALL	Penn	Phase II study of redirected autologous T cells engineered to contain anti-CD19 attached to TCRζ and 4-1BB signaling domains in patients with chemotherapy resistant or refractory acute lymphoblastic leukemia	ARGUS
CTL019B2102J (UPCC-04409) N³=20	Adult CLL and Adult ALL	Penn	Pilot study of redirected autologous T cells engineered to contain anti-CD19 attached to TCRζ and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma	Final CSR

The safety evaluation is based primarily on the pooled data from the single-arm, multicentre Studies CTL019B2202 (n=75) and CTL019B2205J (n=29), in which 104 paediatric and young adult patients (aged ≥ 3 years at screening to aged ≤ 21 years at the time of initial diagnosis) with r/r B-cell ALL were treated with a single tisagenlecleucel infusion. Pooling of Studies CTL019B2202 and CTL019B2205J is supported by the nearly identical study designs, and enrolled identical patient populations.

AEs suspected to be related to study drug were reported in 95.2% of patients. Grade 3 and 4 events were reported as the maximum grade in 26.0% and 48.1% patients respectively, any time post infusion. CRS was always considered to be related to study drug.

Table 20 AEs post- tisagenlecleucel infusion (>15% all patients/all grades) suspected to be study drug related

	Study B2202 N=75			Study B2205J N=29			All patients N=104		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of patients with at least one AE	71 (94.7)	20 (26.7)	35 (46.7)	28 (96.6)	7 (24.1)	15 (51.7)	99 (95.2)	27 (26.0)	50 (48.1)
Cytokine release syndrome	58 (77.3)	16 (21.3)	19 (25.3)	26 (89.7)	5 (17.2)	6 (20.7)	84 (80.8)	21 (20.2)	25 (24.0)

Post-tisagenlecleucel infusion SAEs were reported in 77.9% of infused patients; this high frequency is primarily due to the proportion of patients with CRS (64.4%). Febrile neutropenia was reported in 25 (24%) patients; grade 3 in 24 (23.1%) patients and grade 4 in 1 patient. Grade 3/4 hypotension was reported in 12 (13.2%) patients, and is a known consequence of CRS.

Table 21 SAEs post- tisagenlecleucel infusion regardless of study drug relationship >3 patients all patients / all grades in SCS pool (Safety set)

	Study B2202 N=75			Study B2205J N=29			All patients N=104		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of patients with at least one SAE	58 (77.3)	21 (28.0)	33 (44.0)	23 (79.3)	8 (27.6)	13 (44.8)	81 (77.9)	29 (27.9)	46 (44.2)
Cytokine release syndrome	47 (62.7)	15 (20.0)	19 (25.3)	20 (69.0)	5 (17.2)	6 (20.7)	67 (64.4)	20 (19.2)	25 (24.0)

CRS was the most frequently reported AESI within 8 weeks post-tisagenlecleucel infusion (80.8%) (all events suspected to be study drug related), with no CRS events occurring >8 weeks post-tisagenlecleucel infusion.

CRS events were reported with PTs of CRS (n=84) and histiocytosis hematophagic (n=5). Grade 3/4 events were reported in 46 (44.2%) patients. No patients died due to CRS.

CRS events occurred in median of 3.0 days (1-22 days) post-tisagenlecleucel infusion and the median duration was 8.0 days (range 1-36 days). Grade 3/4 events occurred at a median of 6.0 days (range 2-33 days) post-tisagenlecleucel infusion (Table 5-3).

The time course of onset of CRS after tisagenlecleucel infusion is reflected by the rise of inflammatory and cytokine parameters. Of note, all percentages are based on the number of patients with CRS. Only the first CRS episode is summarised for each patient.

Anti-cytokine therapy was received by 35 (41.7%) of the patients with CRS, tocilizumab was administered to all 35 patients; 19 of whom required only 1 dose of tocilizumab. Five patients (6%) received siltuximab and 19 patients (23%) had treatment with corticosteroids in addition to other anti-cytokine drugs.

Table 22: Anti-cytokine therapy during CRS (Safety set – patients with CRS)

	Study B2202 N=58	Study B2205J N=26	All patients N=84
Systemic anti-cytokine therapy given - n (%)	28 (48.3)	7 (26.9)	35 (41.7)
Tocilizumab	28 (48.3)	7 (26.9)	35 (41.7)
1 dose	17 (29.3)	2 (7.7)	19 (22.6)
2 doses	8 (13.8)	2 (7.7)	10 (11.9)
3 doses	3 (5.2)	3 (11.5)	6 (7.1)
4 doses	0	0	0
>4 doses	0	0	0
Siltuximab	5 (8.6)	0	5 (6.0)
Corticosteroids	14 (24.1)	5 (19.2)	19 (22.6)
Other	2 (3.4)	5 (19.2)	7 (8.3)

Source: [SCS Appendix 1-Table 3-14.1]

2.4.3.2. Yescarta (axicabtagene ciloleucel, KTE-C19) Clinical data evaluation with focus on CRS

The integrated dataset comprises 119 subjects: 108 subjects with refractory aggressive B-cell NHL treated in Phase 1 and Phase 2 of ZUMA-1 and 11 subjects with relapsed/refractory mantle cell lymphoma (MCL) treated in ZUMA-2. Additional preliminary safety data are summarised separately for 11 adult subjects (≥ 18 years of age) and 4 paediatric subjects (2 to 21 years of age, inclusive) with B-precursor ALL treated in ZUMA-3 and ZUMA-4, respectively.

Table 23: Studies providing data on CRS

Study ID	Phase	Study Design	Population Details	Investigational Product/ Target Dose	Enrolled; Completed	Key Endpoints	Status	Data Cutoff Date for CSS/ISS	Pooled (Y/N)
INTEGRATED									
KTE-C19-101 (ZUMA-1)	1/2	Open-label; safety and efficacy; multicenter	Refractory[1] DLBCL, PMBCL, and TFL (adults ≥ 18 y) Phase 1 All disease types Phase 2: Cohort 1: DLBCL Cohort 2: PMBCL + TFL	Conditioning chemotherapy[2] Axicabtagene ciloleucel; 2 × 10^6 cells/kg	Phase 1: 8 leukapheresed; 7 treated Phase 2: 111 leukapheresed 101 treated	Across studies: AEs; SAEs; identified risks (CRS, neurologic events, cytopenias, infections); and potential risks (TLS, secondary malignancy, autoimmune disease, and immunogenicity[7]); laboratory findings; RCR status	Phase 2 Cohort 1 and Cohort 2 completed Phase 3 Cohort 3 Ongoing[1]	31 Dec 2016	Yes
KTE-C19-102 (ZUMA-2)	2	Open-label; safety and efficacy; multicenter	Relapsed/refractory MCL (adults ≥ 18 y)	Conditioning chemotherapy[2] Axicabtagene ciloleucel or KTE-C19 (XLP)[3] 2 × 10^6 cells/kg	16 leukapheresed 11 treated		Ongoing	31 Dec 2016	Yes
SUPPORTIVE									
KTE-C19-103 (ZUMA-3)	1/2	Open-label; safety and efficacy; multicenter	Relapsed/refractory adult B-precursor ALL (≥ 18 y)	Conditioning chemotherapy[2] KTE-C19 (XLP)[3]; 1 to 2 × 10^6 cells/kg	12 leukapheresed 11 treated		Ongoing	31 Dec 2016	No
KTE-C19-104 (ZUMA-4)	1/2	Open-label; safety and efficacy; multicenter	Relapsed/refractory pediatric B-precursor ALL (2 to 21 y, inclusive)	Conditioning chemotherapy[2] KTE-C19 (XLP)[3]; 2 × 10^6 cells/kg	5 leukapheresed 4 treated		Ongoing	31 Dec 2016	No

Table 24 : CRS revised grading system used in axicabtagene ciloleucel studies.

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 ≥ 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

Study Zuma-1

ZUMA-1 is a Phase 1/2 multicentre, open-label study that has evaluated the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL.

Cytokine release syndrome (CRS) is a symptom complex associated with adoptive cell therapies that activate lymphocytes. The goal of CRS management in anti-CD19 CAR T-cell therapy is to prevent life-threatening conditions while preserving the benefits of antitumor effects. In grading CRS, a CRS severity scale associated with antibody therapeutics was published by NCI investigators. Appreciating the scale needed to be adapted for other therapeutics to define mild, moderate, severe, and life-threatening events; account for overlapping symptoms; and guide treatment recommendations, a CRS revised grading system was created by Lee et al. (2014).

Table 25: treatment guidance algorithm

Cytokine Release Syndrome Grading Assessment	Extensive co-morbidities or older age? No/Yes	Treatment
Grade 1: • Fever (defined as ≥ 38.3°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% 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% O_2 • Organ toxicity: grade 2	Yes	• As above for grade 2 • Consider tocilizumab (8 mg/kg intravenously [IV] over 1 hr, not to exceed 800 mg) ± corticosteroids (e.g., methylprednisolone 1 mg/kg BID or dexamethasone 10 mg q6hrs)[b]
Grade 3: • Hypotension: requires multiple vasopressors or high dose vasopressors [a] • Hypoxia: requires ≥ 40% 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 1 g/day x 3, followed by a rapid taper consisting of 250 mg BID x 2 days, 125 mg BID x 2 days and then 60 mg BID x 2 days) [b]

[a] Refer to Table 19 of the KTE-C19-101 Protocol.

[b] Refer to Section 6.4.1 of the KTE-C19-101 Protocol Amendment 5 for recommended doses and details.

All safety analyses were conducted using the safety analysis set. Amongst others, demographic and baseline disease characteristics, and levels of serum cytokines were analysed. AEs events of interest included identified risks (cytokine release syndrome [CRS]; neurologic AEs; cytopenias, including febrile neutropenia; and infection).

Grade 3 or higher CRS occurred in 13% of subjects. All events had an onset within 2 weeks after the infusion of axicabtagene ciloleucel and all resolved, with the exception of the 2 Grade 5 events, both of which followed ongoing CRS events that started within the first week after the cell infusion.

Rates of Grade 3 or higher CRS decreased over the course of the study the incidence of Grade 3 or higher CRS was 18% among the 62 subjects analysed at the second interim analysis and 5% among the 39 subjects enrolled afterwards. The rates of severe adverse reactions decreased over the course of the trial and were managed with supportive care, tocilizumab, and corticosteroids.

Individual symptoms of CRS were graded per CTCAE v4.01. Ninety-four subjects (93%) experienced CRS. The majority of subjects (81%) who experienced CRS had Grade 1 or Grade 2 CRS. Nine subjects (9%) had worst Grade 3 CRS, 3 subjects (3%) had worst Grade 4 CRS, and 1 subject (1%) had a Grade 5 CRS.

The most common CRS symptom of any grade was pyrexia (76%), followed by hypotension (41%), hypoxia (22%), tachycardia (21%), and chills (20%). Most of these events were Grade 1 or Grade 2. The most common Grade 3 or higher CRS events were pyrexia (11%), hypotension (9%), and hypoxia (9%).

Among the 93 subjects whose symptoms resolved, the median time to resolution of CRS symptoms was 8 days.

As of the data cut-off date (27 Jan 2017), CRS events had resolved in 98% of subjects, with the exceptions of HLH and anoxic brain injury in the setting of CRS, both of which resulted in the subject's death.

Table 26 : Incidence of CRS in > 5% of patients in cohort 1 and 2 (SAS n= 101)

Event n(%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
CRS – Any (1)	94 (93)	37 (37)	44 (44)	9 (9)	3 (3)	1 (1)
Pyrexia	77 (76)	13 (13)	53 (52)	11 (11)	0 (0)	0 (0)
Hypotension	41 (41)	9 (9)	23 (23)	9 (9)	0 (0)	0 (0)
Hypoxia	22 (22)	1 (1)	12 (12)	8 (8)	1 (1)	0 (0)
Tachycardia	21 (21)	19 (19)	1 (1)	1 (1)	0 (0)	0 (0)
Chills	20 (20)	16 (16)	4 (4)	0 (0)	0 (0)	0 (0)
Sinus tachycardia	8 (8)	6 (6)	2 (2)	0 (0)	0 (0)	0 (0)
Headache	5 (5)	3 (3)	2 (2)	0 (0)	0 (0)	0 (0)

Abbreviations: CRS, cytokine release syndrome.
Note: Preferred terms are sorted in descending order of total frequency count. Percentages are calculated using the total number of subjects in the treatment group as the denominator.
(1) CRS syndrome was graded based on the revised grading system of Lee et al, 2014. Individual symptoms (MedDRA Version 19.0 preferred terms) are graded per CTCAE 4.03.

ZUMA-1 and ZUMA-2 with supportive data from ZUMA-3 and ZUMA-4

Among all 119 subjects, 110 subjects (92%) had CRS. Worst Grade 1 or Grade 2 CRS was observed in 94 subjects (79%); worst Grade 3 CRS was observed in 11 subjects (9%); worst Grade 4 CRS was observed in 4 subjects (3%), and a Grade 5 CRS (HLH) was observed in 1 subject. Overall, 16 subjects (13%) had Grade ≥ 3 CRS.

Grade 3 or higher CRS symptoms reported in ≥10% of subjects were pyrexia (15 subjects, 13%), hypotension (12 subjects, 10%), and hypoxia (13 subjects, 11%). No subject had new onset CRS that started > 14 days after the cell infusion. Two subjects, 1 with anoxic brain injury and 1 with HLH, died after Day 30 due to events that occurred in the setting of CRS.

Table 27: CRS in > 10% of patients in ZUMA-1 and ZUMA-2

	Overall (N = 119)				
	Subjects With Worst Grade (n [%])				
MedDRA Preferred Term	Any	1-2	3	4	5
Subjects with any AE[1]	110 (92)	94 (79)	11 (9)	4 (3)	1 (1)[2]
Pyrexia	94 (79)	79 (66)	15 (13)	0	0
Hypotension	46 (39)	34 (29)	12 (10)	0	0
Hypoxia	25 (21)	11 (9)	13 (11)	1 (1)	0
Chills	24 (20)	24 (20)	0	0	0
Tachycardia	23 (19)	22 (18)	1 (1)	0	0
Sinus tachycardia	10 (8)	10 (8)	0	0	0

Table 28: CRS events in >1 subject ZUMA 3 and ZUMA 4

MedDRA Preferred Term	ZUMA-3 (N = 11)					ZUMA-4 (N = 4)				
		Subjects With Worst Grade (n [%])					Subjects With Worst Grade (n [%])			
	Any	1-2	3	4	5	Any	1-2	3	4	5
Subjects with any AE[1]	11 (100)	8 (73)	3 (27)	0	0	4 (100)	1 (25)	3 (75)	0	0
Pyrexia	8 (73)	5 (45)	3 (27)	0	0	4 (100)	1 (25)	3 (75)	0	0
Hypotension	6 (55)	4 (36)	2 (18)	0	0	4 (100)	1 (25)	3 (75)	0	0
AST increased	3 (27)	1 (9)	2 (18)	0	0	1 (25)	1 (25)	0	0	0
Chills	4 (36)	4 (36)	0	0	0	0	0	0	0	0
ALT increased	3 (27)	1 (9)	2 (18)	0	0	0	0	0	0	0
Blood bilirubin increased	3 (27)	2 (18)	1 (9)	0	0	0	0	0	0	0
Hypoxia	2 (18)	1 (9)	1 (9)	0	0	1 (25)	0	1 (25)	0	0
Sinus tachycardia	3 (27)	3 (27)	0	0	0	0	0	0	0	0
Blood ALP increased	2 (18)	2 (18)	0	0	0	0	0	0	0	0
Febrile neutropenia	2 (18)	0	2 (18)	0	0	0	0	0	0	0
Hyponatraemia	2 (18)	2 (18)	0	0	0	0	0	0	0	0

Table 29 Grade 3 and higher CRS events NCI 09-C-0082

CTCAE Term[1]	NCI-09C-0082 (N = 13)			
	Subjects With Worst Grade (n [%])			
	≥ 3	3	4	5
Subjects with any AE	8 (61.5)	5 (38.5)	3 (23.1)	0
Febrile neutropenia[2]	6 (46.2)	6 (46.2)	0	0
Fever[3]	3 (23.1)	3 (23.1)	0 (0.0)	0
Hypotension	3 (23.1)	0	3 (23.1)	0
Supraventricular and nodal arrhythmia: supraventricular tachycardia	1 (7.7)	0	1 (7.7)	0

Starting from CRS Grade 2, tocilizumab was recommended to be administered at a dose of 8 mg/kg infused IV over 1 hour (dose should not exceed 800 mg) and repeated every 4-6 hours, as needed based on response, up to 3 doses in a 24hr period. If there was no significant improvement with tocilizumab (e.g. no change in grade of CRS), corticosteroids should be administered (e.g. methylprednisolone 1mg/kg BID or dexamethasone 10mg every 6 hours). High doses of corticosteroids (e.g. methylprednisolone 1g/day x3 followed by a rapid taper, based on response, consisting of 250mg BID x2 days, then 125mg BID x2 days and then 60mg BID x2 days) should be considered for life-threatening CRS.

Grade 3 or higher CRS occurred in 13% of subjects. All events had an onset within 2 weeks after the infusion of axicabtagene ciloleucel and all resolved, with the exception of the 2 Grade 5 events, both of which followed ongoing CRS events that started within the first week after the cell infusion. Cardiac rhythm and cardiac failure disorders were observed in the setting of CRS. All cardiac events in the setting of CRS resolved.

Table 30: Summary of tocilizumab use - SAS

	Phase 2		
	Cohort 1 (N=77) n (%)	Cohort 2 (N=24) n (%)	Total (N=101) n (%)
Subjects who took tocilizumab during the study	32 (42)	11 (46)	43 (43)
Tocilizumab were taken to manage AEs	29 (38)	10 (42)	39 (39)
CRS	16 (21)	1 (4)	17 (17)
Pyrexia	9 (12)	1 (4)	10 (10)
Hypotension	9 (12)	0 (0)	9 (9)
Hypoxia	5 (6)	0 (0)	5 (5)
Atrial flutter	2 (3)	0 (0)	2 (2)
Tachycardia	2 (3)	0 (0)	2 (2)
Acute kidney injury	1 (1)	0 (0)	1 (1)
Atrial fibrillation	1 (1)	0 (0)	1 (1)
Chills	1 (1)	0 (0)	1 (1)
Respiratory rate increased	1 (1)	0 (0)	1 (1)
Sinus tachycardia	1 (1)	0 (0)	1 (1)

Table 31: Concomitant Medications - SAS

	Phase 1 (N=7)	Phase 2		
		Cohort 1 (N=77)	Cohort 2 (N=24)	Total (N=101)
Steroids [1]				
Any	4 (57)	21 (27)	6 (25)	27 (27)
Used for treatment of CRS	0 (0)	5 (6)	1 (4)	6 (6)
Used for treatment of NE	3 (43)	11 (14)	4 (17)	15 (15)
Other use	4 (57)	14 (18)	3 (13)	17 (17)
Tocilizumab				
Any	6 (86)	32 (42)	11 (46)	43 (43)
Used for treatment of CRS	1 (14)	16 (21)	1 (4)	17 (17)
Used for treatment of NE	6 (86)	23 (30)	10 (42)	33 (33)
Other use	1 (14)	4 (5)	1 (4)	5 (5)
Steroids or Tocilizumab				
Any	6 (86)	34 (44)	11 (46)	45 (45)
Steroids and Tocilizumab				
Any	4 (57)	19 (25)	6 (25)	25 (25)

***Supportive studies:* Literature Search**

The first report of TCZ being used successfully to treat CRS involved a 7-year-old female patient with ALL, who experienced severe CRS after receiving CTL019, an investigational second-generation CD19 CAR T-cell therapy (Grupp et al. 2013). Cytokine blockade with TCZ and etanercept resulted in a marked decrease in elevated cytokine and cytokine receptor levels and was effective in rapidly reversing severe/life-threatening CRS without affecting expansion of CAR T-cells or reducing anti-leukemic efficacy.

Another report appeared of a patient successfully treated with TCZ for CRS, this time a 7-year-old male patient with B-ALL who developed CRS/HLH following blinatumomab therapy (Teachey et al. 2013).

At least 55 patients reported in the literature to have received TCZ for the treatment of CRS following either CAR T-cell therapy (54 patients) or bispecific T-cell-engaging therapy (blinatumomab, 1 patient) (Table 3).

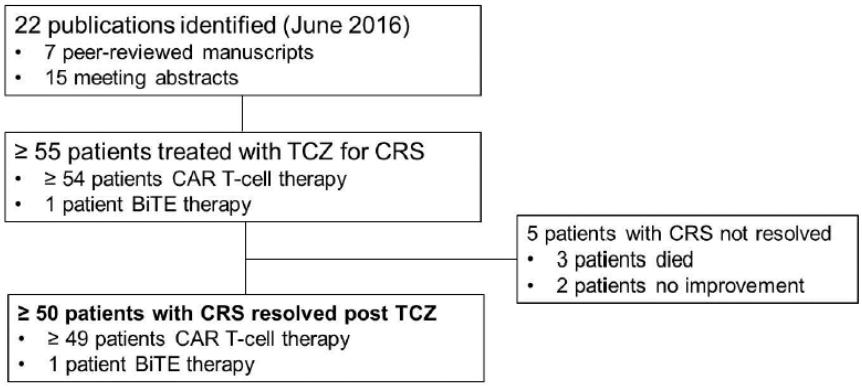
Methods

A comprehensive search using PubMed was conducted by the MAH to identify publications on the use of TCZ for the treatment of CRS. Only those publications in which TCZ was stated to have been used (successfully or unsuccessfully) as a treatment for CRS were included. In addition, the ClinicalTrials.gov and NIH GeMCRIS database were searched for clinical trials investigating TCZ for the treatment of CRS, and reviewed the transcript and video of the NIH Recombinant DNA Advisory Committee symposium on Cytokine Release Syndrome after T-cell Immunotherapy held on June 10, 2015 (Recombinant DNA Advisory Committee Meeting, 2015).

The literature search was conducted in June 2016. This search strategy yielded 22 publications, 20 of which originated from the US (7 peer-reviewed manuscripts, 13 meeting abstracts) and 2 from China (2 meeting abstracts).

From these publications, at least 55 patients had been treated with TCZ for CRS, of which at least 50 patients had been treated successfully (see figure below).

Figure 8: Overview of Literature search results: CRS after T-cell Immunotherapy



The presentations from the American Society of Hematology (ASH) meeting held in December 2016 and the American Association for Cancer Research (AACR) held in April 2017 were reviewed to update the literature search with results from two recently completed phase II trials, namely the pivotal ELIANA study evaluating tisagenlecleucel-T (CTL019; Grupp et al. 2016), and the pivotal ZUMA-1 study evaluating axicabtagene ciloleucel (KTE-C19; Locke et al. 2017).

Treatments

The marketed IV formulation of TCZ (Actemra/RoActemra solution for infusion) from commercial sources was used in the literature reports describing use of TCZ as a treatment for CRS.

Results

Table 32: Tocilizumab treatment of CRS following CAR-T and bispecific immunotherapy

Publication	Affiliation	Immunotherapy	Indication	No. of Patients Treated with TCZ (TCZ Dosing Regimen)	CRS Outcome Post-TCZ
Grupp et al. 2013 (*Manuscript*)	Children's Hospital of Philadelphia; University of Pennsylvania; NOVARTIS	CTL019 (2nd generation CD19 CAR [CD137/CD3])	Pediatric ALL	1 patient TCZ+ETN+CS (TCZ 8 mg/kg × 1)	1/1 resolved [a]
Teachey et al. 2013 (*Manuscript*)	Children's Hospital of Philadelphia; University of Pennsylvania; AMGEN	Blinatumomab (BiTE)	Pediatric ALL	1 patient TCZ+CS (TCZ 8 mg/kg × 1)	1/1 resolved
Maude et al. 2014 (*Manuscript*)	Children's Hospital of Philadelphia; University of Pennsylvania; NOVARTIS	CTL019	Pediatric and young adult ALL	9 patients TCZ only, 3 patients; TCZ+CS, 6 patients 4 patients received TCZ × 2 (TCZ dose not reported)	9/9 resolved [a]
Grupp et al. 2014 (*Abstract*)	Children's Hospital of Philadelphia; University of Pennsylvania; NOVARTIS	CTL019	Pediatric and young adult ALL	11 patients TCZ only, 6 patients; TCZ+CS, 5 patients (TCZ dose/no. of doses not reported)	11/11 resolved [a]
Grupp et al. 2015 (*Abstract*)	Children's Hospital of Philadelphia; University of Pennsylvania; NOVARTIS	CTL019	Pediatric and young adult ALL	15 patients TCZ only, 6 patients, TCZ+CS, 9 patients (TCZ dose/no. of doses not reported)	15/15 resolved [a]

Frey et al. 2014 (*Abstract*)	Children's Hospital of Philadelphia; University of Pennsylvania; NOVARTIS	CTL019	Adult ALL	9 patients Details provided for 3 refractory patients only: TCZ+CS, 1 patient (TCZ 4 mg/kg × 2); TCZ+ETN+CS, 1 patient (TCZ 8 mg/kg × 3) ; TCZ+STX+CS, 1 patient (TCZ 8 mg/kg × 2, STX × 2)	6/9 resolved 3/9 died [b]
Porter et al. 2014a (*Abstract*)	Children's Hospital of Philadelphia; University of Pennsylvania; NIH; NOVARTIS	CTL019	Adult CLL	7 patients TCZ ± CS, 7 patients; several patients also received CS and/or ETN (TCZ dose/no. of doses not reported)	7/7 resolved [c]
Porter et al. 2014b (*Abstract*)	Children's Hospital of Philadelphia; University of Pennsylvania; NOVARTIS	CTL019	Adult CLL	3 patients TCZ ± CS ± anti-cytokine therapy (TCZ dose/no. of doses not reported)	3/3 resolved [c]
Porter et al. 2015 (*Manuscript*)	Children's Hospital of Philadelphia; University of Pennsylvania; NOVARTIS	CTL019	Adult CLL	4 patients TCZ only, 2 patients; TCZ+CS, 2 patients (TCZ dose/no. of doses not reported)	4/4 resolved [c]
Lee et al. 2014b (*Abstract*)	NCI; NIH; Children's Hospital Los Angeles	2nd generation CD19 CAR [CD28/CD3]	ALL, NHL	4 patients TCZ alone, 2 patients; TCZ+CS, 2 patients (TCZ dose/no. of doses not reported)	4/4 resolved [d]
Lee et al. 2015a (*Manuscript*)	NCI, NIH, Children's Hospital Los Angeles; University of California, Los Angeles	2nd generation CD19 CAR [CD28/CD3]	Pediatric and young adult ALL, NHL	4 patients TCZ alone, 2 patients; TCZ+CS, 2 patients (TCZ dose/no. of doses not reported)	4/4 resolved [d]
Davila et al. 2014 (*Manuscript*)	Memorial Sloan Kettering Cancer Center, New York City; JUNO	2nd generation CD19 CAR [CD28/CD3]	Adult B-ALL	4 patients TCZ alone × 1, 1 patient; TCZ alone × 2, 2 patients; TCZ+CS × 1, 1 patient (TCZ dose not reported)	4/4 resolved [e]
Park et al. 2014 (*Abstract*)	Memorial Sloan Kettering Cancer Center, New York City; JUNO	2nd generation CD19 CAR [CD28/CD3]	Adult B-ALL	9 patients IL-6R antagonist or CS (TCZ dose/no. of doses not reported)	9/9 resolved [e,f]
Curran et al. 2014 (*Abstract*)	Memorial Sloan Kettering Cancer Center, New York City; JUNO	2nd Generation CD19 CAR [CD28/CD3]	Pediatric and young adult B-ALL	2 patients TCZ or CS (TCZ dose/no. of doses not reported)	2/2 resolved [g]

Curran et al. 2015 (*Abstract*)	Memorial Sloan Kettering Cancer Center, New York City; Dana-Farber Cancer Institute and Boston Children's Hospital, Boston; JUNO	2nd Generation CD19 CAR [CD28/CD3]	Pediatric and young adult B-ALL	5 patients TCZ or CS (TCZ dose/no. of doses not reported)	5/5 resolved [g]
Sauter et al. 2014 (*Abstract*)	Memorial Sloan Kettering Cancer Center, New York City; JUNO	2nd Generation CD19 CAR [CD28/CD3] after SCT	Adult B-NHL	2 patients TCZ only 4 mg/kg × 1, 1 patient; TCZ+CS, 1 patient (TCZ dose/no. of doses not reported)	2/2 resolved
Schuster et al. 2014 (*Abstract*)	Perelman Center for Advanced Medicine and University of Pennsylvania; NOVARTIS	CTL019	Adult NHL	1 patient TCZ+CS (TCZ dose/no. of doses not reported)	1/1 resolved [h]
Kochenderfer et al. 2015 (*Manuscript*)	NCI, NIH, Hackensack University Medical Center, New Jersey; MD Anderson Cancer Center, Texas; Sunnybrook Odette Cancer Center, Canada; KITE PHARMA	2nd generation CD19 CAR [CD28/CD3]	Adult DLBCL or indolent B-cell malignancy	2 patients TCZ only (TCZ dose/no. of doses not reported)	2/2 did not improve [i]
Brudno and Kochenderfer, 2016 (*Abstract*)	NCI	CD269 CAR CD19 CAR	Adult ALL	2 patients TCZ × 2, 1 patient TCZ × 1, 1 patient (TCZ dose not provided)	2/2 improved
Lee et al. 2015b (*Abstract*)	NCI, NIH	2nd generation CD19 CAR [CD28/CD3]	Pediatric and young adult ALL	1 patient TCZ+CS (TCZ dose/no. of doses not reported)	1/1 resolved
Locke et al. 2015 (*Abstract*)	4 hospitals in the US; KITE PHARMA	KTE-C19 (2nd generation CD19 CAR [CD28/CD3])	Adult NHL	1 patient TCZ+CS (TCZ dose/no. of doses not reported)	Not provided but assumed resolved [j]
Dong et al. 2015 (*Abstract*)	14 hospitals in China; AMERICA YUVA BIOMED	4SCAR19 (4th generation CD19 CAR [CD28/CD137/ CD27/CD3])	Adult and pediatric ALL	11 patients ETN or TCZ, 8 patients ETN+TCZ, 3 patients (ETN 12.5 mg, TCZ 8 mg/kg, no. of doses not reported)	Not provided, but assumed resolved [k,l]
Luo et al. 2015 (*Abstract*)	2 hospitals in China, 1 hospital in the US; AMERICA YUVA BIOMED	4SCAR123 (4th generation CD123 CAR [CD28/CD137/ CD27/CD3])	Adult AML	1 patient TCZ only (TCZ dose/no. of doses not reported)	1/1 resolved

Total from literature search (June 2016):					
Publications: 22	**Publications:** 20 from US (7 peer-reviewed manuscripts, 13 meeting abstracts); 2 from China (2 meeting abstracts)	**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 TCZ:** ≥ 55 patients Where provided: TCZ × 1, 10 patients; TCZ × 2, 9 patients; TCZ × 3, 1 patient Where provided: 8 mg/kg, 12 patients; 4 mg/kg; 2 patients	**CRS Resolved:** ≥ 50 patients

Table 33: Summary from the pivotal trials of axicabtagene ciloleucel and tisagenlecleucel-T presented at ASH 2016 and AACR 2017

Pivotal Phase II trials of tisagenlecleucel-T (CTL019; Novartis) and axicabtagene ciloleucel (KTE-C19; Kite Pharma, Inc.)[m]					
Grupp et al. 2016 (*Abstract*); phase II ELIANA study	25 hospitals in the US/EU, Canada, Australia, and Japan; NOVARTIS	CTL019	Adult and pediatric ALL	25 patients	Complete resolution of all CRS events
Locke et al. 2017 (*Abstract*); phase II ZUMA-1 study	22 hospitals; KITE PHARMA	KTE-C19	Adult NHL	43 patients TCZ 27 patients steroids	CRS reversible except for 1 case of HLH and 1 case of cardiac arrest

Davila et al. reported that administration of tocilizumab as a first-line therapy for sCRS in patients MSK-ALL13, MSK-ALL14, and MSK-ALL17 similarly reduced fevers and ameliorated clinical symptoms without apparent effect on 19-28z CAR-T cell expansion and persistence. However, a decrease in CAR-T cells was also observed in some patients.

Figure 9: The effects of steroids and /or tocilizumab on the expansion of CAR-T cells in CRS patients.

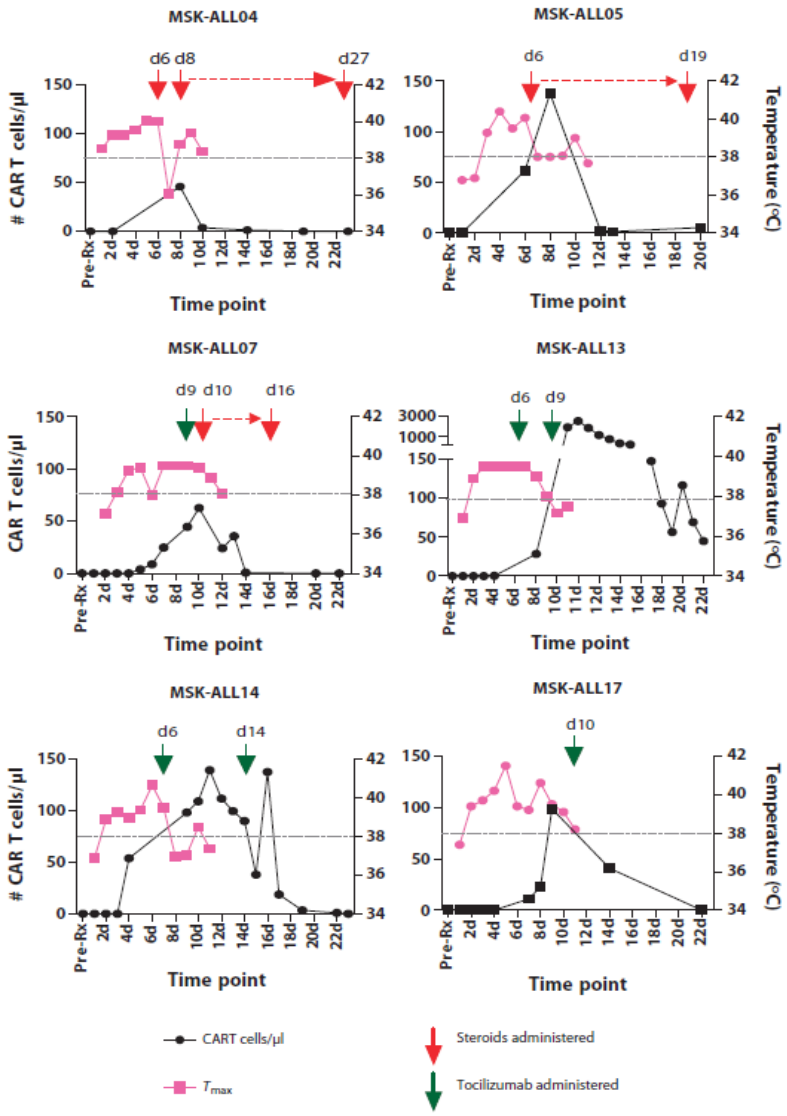
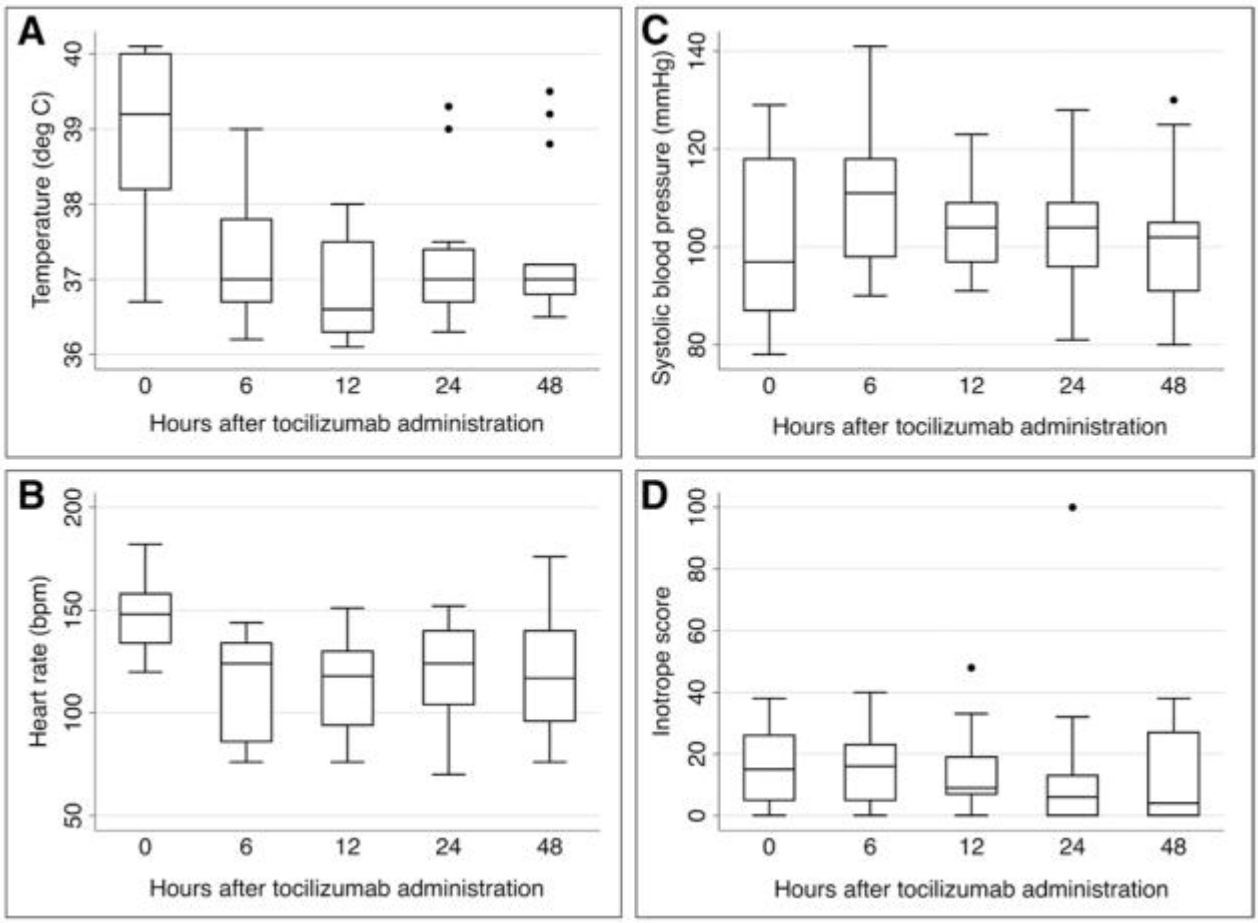


Fig. 2. The effect of steroids and/or tocilizumab on the expansion of CAR T cells in patients with sCRS. The number of CAR T cells per microliter of whole blood, detected by qPCR, was measured in samples drawn before treatment and from days 1 to 22 after CAR T cell infusion. Max temperatures on days 1 to 11 are also depicted. In addition, the days when steroids or tocilizumab was administered to manage sCRS are shown. The red dashed line represents the duration of steroid treatment, and the gray dashed line is at the 38°C fever threshold.

Figure 10: Changes in A, temperature; B, heart rate; C, systolic blood pressure; and D), inotrope score after tocilizumab administration (n = 14). $p < 0.05$ for all changes in heart rate and temperature compared to time 0 (tocilizumab administration). (Fitzgerald et al 2017)



2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The proposed indication is supported by the clinical data relevant to patients treated with tocilizumab following the administration of CAR-T cell therapies. It is further substantiated by published data (either full-text manuscripts or conference abstracts) describing the effectiveness of tocilizumab in treating severe or life-threatening CRS.

Efficacy data and additional analyses

The efficacy of RoActemra for the treatment of CRS was assessed in a retrospective analysis of data from clinical trials of CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) for haematological 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 first episode of CRS was included in the analysis. The efficacy population for the tisagenlecleucel cohort included 28 males and 23 females (total 51 patients) of median age 17 years (range, 3–68 years). The median time from start of CRS to first dose of tocilizumab was 3 days (range, 0–18 days). 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, if no more than 2 doses of RoActemra were needed, and no drugs other than RoActemra and corticosteroids were used for treatment. Thirty-nine patients (76.5%; 95% CI: 62.5%–87.2%) achieved a response with no more than 2 doses of TCZ. In an independent cohort of 15 patients (range: 9–75 years old) with axicabtagene ciloleucel-induced CRS, 53% responded with no more than 2 doses of TCZ.

The studies evaluating CAR-T treatments were not planned for the evaluation of the effect of tocilizumab on CRS and no direct comparisons can be made. Furthermore, co-medication with corticosteroids was allowed, and no subgroup analysis for patients treated with / without corticosteroids was foreseen. However, the observations of rapid effects on objective early endpoints, such as vital signs (Fitzgerald et al 2017; Brudno et al 2016; Davila et al 2014) provided significant evidence on the role of tocilizumab in the resolution of this life threatening adverse event.

Overall, data indicate that following a treatment guidance algorithm for CRS management CRS can be resolved. These algorithms included vigilant supportive care, including empiric treatment of concurrent bacterial infections and maintenance of adequate hydration and blood pressure. This standard therapy was recommended for every grade of CRS. Additional treatment specifically directed to resolving the CRS (e.g. corticosteroids or tocilizumab) was to be given for higher grades of CRS.

Using the approved dose regimens in adults (RA) and children (sJIA and pJIA) as a guide, the MAH proposes a posology for treatment of CRS given as a 60-minute intravenous infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg - with an option to repeat for up to 3 additional doses if clinical improvement did not occur within 24 to 48 h. RoActemra can be given alone or in combination with corticosteroids. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients.

Further discussion is needed to explore the possibility of collecting and sharing data on the use of tocilizumab (such as data from registries) across actual- and future- MAH of CAR-T cell products – in the context of the next revision of the RMP.

2.4.4. Conclusions on the clinical efficacy.

Data submitted demonstrate efficacy of tocilizumab in the resolution of CRS due to CAR-T therapy. The proposed posology is based on the previously observed safe blood concentrations in clinical studies in the clinical development program for TCZ. In higher grade CRS, co-administration with corticosteroids and other concomitant medication might be needed.

Discussion focusing on the possibility of collecting and sharing data on the use of tocilizumab in the management of CRS due to CAR-T therapy – across MAHs for the respective products will be addressed in the next RMP revision (due 22.08.18 - either within a parallel variation or as a standalone submission).

2.5. Clinical safety

Introduction

The safety of tocilizumab has been well characterised in patients with rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (PJIA), and systemic juvenile idiopathic arthritis (SJIA). The safety of tocilizumab in the proposed CRS indication is evaluated based on observed safe blood concentrations in pharmacology studies in connection with the known safety profile of tocilizumab.

Patient exposure

See clinical efficacy section for available data on patient exposure from published literature.

Adverse events

Discussion on exposure-safety relationship focusses on neutropenia. Additionally, exposure relationships were investigated for SAEs and AEs by system organ class (see Clinical Pharmacology section).

No additional safety concerns for patients receiving TCZ in the treatment are anticipated.

Serious adverse event / deaths / other significant events

See discussion on exposure – safety relationship (Clinical Pharmacology and Clinical Safety).

Laboratory findings

The following safety laboratory parameters were investigated in the context of exposure – safety analyses: For haematology: haemoglobin, white blood cells, neutrophil, eosinophil and lymphocyte counts, platelets. For biochemistry: alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, serum albumin, total protein, total cholesterol, cholesterol-HDL, cholesterol-LDL, triglycerides.

No new findings in terms of laboratory investigations specific to tocilizumab were observed.

Safety in special populations

See discussion on the paediatric population under Clinical pharmacology.

Safety related to drug-drug interactions and other interactions

No specific DDI studies have been conducted

Discontinuation due to adverse events

No data on discontinuation of tocilizumab due to adverse events were reported.

Post marketing experience

Not applicable.

2.5.1. Discussion on clinical safety

The safety of tocilizumab has been well characterised in patients with rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (PJIA), and systemic juvenile idiopathic arthritis (SJIA) in adults and paediatric populations above the age of 2 years. The safety of tocilizumab in the proposed CRS indication and posology can solely be evaluated based on previously observed safe blood concentrations and the known safety profile of tocilizumab.

From the CAR T-cell trials the pharmacokinetics (PK) data were available for 27 patients after the first dose of TCZ and for 8 patients after a second dose of TCZ. The PK population included 15 male and 12 female patients of median age 12 years (range, 4-23 years). The geometric mean (% CV) maximum concentration of TCZ in the patients with CAR T-cell-induced, severe or life-threatening CRS was 99.5 μg/mL (36.8%) after the first infusion and 160.7 μg/mL (113.8%) after the second infusion.

The results of the simulations suggested that TCZ concentrations after up to 4 doses given 8 hours apart would remain within the bounds of previously observed safe blood concentrations, e.g. clinical studies in the clinical development program for TCZ (see also Clinical Pharmacology). A comparison of AEs across AUC_{2weeks} exposure quartiles in Study WA18221 revealed no trend towards an increased incidence in the percentage of patients reporting at least one AE with increasing TCZ exposure. When comparing SAEs across AUC_{2weeks} exposure quartiles most SAEs occurred in the first exposure quartile indicating that there was no trend towards an increased incidence in percentage of patients with SAEs with increasing TCZ exposure. With respect to neutropenia, more severe neutropenia was observed with higher TCZ exposures. However, this finding as well as the overall paediatric safety profile was consistent with the known TCZ safety profile in the adult population and thus, the same conclusion may be drawn.

No reports on adverse drug reactions due to tocilizumab administration were received in the context of the trials reviewed. Since there was no way to differentiate between adverse events caused by CAR-T cell therapies from any adverse events potentially caused by tocilizumab, the following statement has been included in section 4.8 of the RoActemra IV SmPC as follows:

“The safety of tocilizumab in CRS has been evaluated in a retrospective analysis of data from clinical trials, where 51 patients were treated with intravenous tocilizumab 8 mg/kg (12 mg/kg for patients less than 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CAR T-cell-induced CRS. A median of 1 dose of tocilizumab (range, 1-4 doses) was administered”.

A discussion on the possibility of collecting and sharing safety data with the use of tocilizumab (such as spontaneous reports to the MAH and data from registries) across actual- and future- MAH of CAR-T cell products, will be included in the next revision of the RMP.

2.5.2. Conclusions on clinical safety

The safety profile of tocilizumab is well known. No new safety findings have been reported.

Given the low number of patients exposed to higher doses the applicant is asked to further characterise the safety of tocilizumab in the treatment of patients with chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome post authorisation. Data on the timing of tocilizumab administration relative to the nature and onset of adverse events should be collected.

The MAH will include proposed relevant measures in the upcoming RMP revision either within a parallel variation or as a standalone submission).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

No risk management plan was submitted. The risk management plan version is being revised in the context of the ongoing procedure II/76.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cytokine release syndrome is an expected AE in patients infused with tisagenlecleucel or axicabtagene ciloleucel as a class-effect of T-cell directed therapies and an on-target effect related to the mechanism of action.

3.1.2. Available therapies and unmet medical need

CAR-T therapy is an emerging promising option in oncology patients -with the most serious safety concern being the risk of developing CRS. Treatment of cytokine release syndrome as an ADR of CAR-T cell therapies is based on a severity grading scale and a specific algorithm. Multiple approaches have been used to treat low grade CRS, however severe CRS is a medical emergency and requires prompt and effective treatment to avoid serious complications or fatal outcome. There is therefore a high unmet medical need for an effective treatment for severe or life-threatening CRS following CAR-T cell therapy, to ensure safe use of this novel treatment in oncology patients.

3.1.3. Main clinical studies

A retrospective analysis of data from clinical trials of CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) for haematological malignancies was performed. 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 episode of CRS was included in the analysis.

3.2. Favourable effects

The efficacy population for the tisagenlecleucel cohort included 28 males and 23 females (total 51 patients) of median age 17 years (range, 3–68 years). The median time from start of CRS to first dose of tocilizumab was 3 days (range, 0–18 days). 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, if no more than 2 doses of RoActemra were needed, and no drugs other than RoActemra and corticosteroids were used for treatment. Thirty-nine patients (76.5%; 95% CI: 62.5%–87.2%) achieved a response. In an independent cohort of 15 patients (range: 9–75 years old) with axicabtagene ciloleucel-induced CRS, 53% responded.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties about the favourable effects of tocilizumab in the resolution of CRS due to CAR-T therapy.

3.4. Unfavourable effects

No new unfavourable effects have been reported.

3.5. Uncertainties and limitations about unfavourable effects

There were no specific assessments for the safety of tocilizumab in these settings. However, there were no reports of adverse reactions to tocilizumab in patients studied. Further collection of data will be addressed in the next revision of the RMP.

Given the low number of patients exposed to higher doses the applicant is asked to further characterise the safety of tocilizumab in the treatment of patients with chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome post authorisation. Data on the timing of tocilizumab administration relative to the nature and onset of adverse events should be collected.

3.6. Effects Table

Table 34: Effects Table for tocilizumab in CRS due to CAR-T therapy in the retrospective analysis of CTL 019 and KTE-C19 studies.

Effect	Short description	Unit	Treatment Tocilizumab (iv)	Control	Uncertainties / Strength of evidence	References Le et al The Oncologist 2018-0028
Favourable Effects						
Resolution of CRS by 2 doses of TCZ	lack of fever / off vasopressors for at least 24h	N (%)			76.5%; 95% CI: (62.5%–87.2%)	Le et al theoncologist.2018-0028.
Primary analysis: By day 14	**CTL019**		31 (68.9)		(53.4 – 81.8)	
	KTE-C19		8 (53.3)		(26.6 – 78.7)	
By day 2	**CTL019**		9 (20.0)		(9.6 – 34.6)	
	KTE-C19		3 (20)		(4.3 – 48.1)	
By day 7	**CTL019**		26 (57.8)		(42.2 – 72.3)	
	KTE-C19		8 (53.3)		(26.6 – 78.7)	
By day 21	**CTL019**		31 (68.9)		(53.4-81.8)	
	KTE-C19		8 (53.3)		(26.6 – 78.7)	
Unfavourable Effects						
As established for RoActemra;						

Abbreviations: CTL019: tisagenlecleucel; KTE-C19: axicabtagene ciloleucel

Notes: In the retrospective study response was determineded at 2 doses of tocilizumab.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Severe or life-threatening CRS following CAR-T cell therapy is a medical emergency, and requires prompt and effective treatment to avoid serious complications or a fatal outcome. There is therefore a high unmet medical need for an effective treatment for CRS, to avoid limiting the use of this emerging, novel and important treatment option. Given the curative potential of CAR-T therapy in oncology patients with limited options and the need to effectively manage the CRS side effect, the favourable effects of tocilizumab largely outweigh the currently known safety profile and any uncertainties.

The proposed posology is based on the previously observed safe blood concentrations in clinical studies in the clinical development program for tocilizumab. In higher grade CRS, co-administration with corticosteroids and other concomitant medication might be needed.

3.7.2. Balance of benefits and risks

Treatment of CRS with tocilizumab as anti-cytokine therapy is effective and can be safely administered in the already approved doses due to the well-known general safety profile of TCZ.

The proposed TCZ dose of 8 mg/kg IV (12 mg/kg IV for patients < 30 kg) administered up to 4 times at least 8 hours apart to be medically justified, and have an appropriate benefit-risk profile.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of RoActemra is positive in the indication 'treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older'.

4. Recommendations

Outcome

Based on the review of the available data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include 'treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older' for the RoActemra 20mg/ml concentrate for solution for infusion. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6.6 the SmPC are updated. The Package Leaflet is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for

under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

An updated RMP shall be submitted by 22nd August, either within a parallel variation or as a standalone submission.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0181/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include 'treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older' for the RoActemra 20mg/ml concentrate for solution for infusion.

Summary

See Scientific Discussion.

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