20 July 2017
EMA/562609/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0066

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ACR	American College of Rheumatologists
AE	adverse events
AESI	adverse event of special interest
BSR/BHPR	British Society for Rheumatology/British Health Professionals in Rheumatology
CRP	C-reactive protein
CTA	computed tomography angiography
EQ-5D	EuroQol 5D health questionnaire
ER	exposure-response
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	Fatigue functional assessment of chronic illness therapy fatigue
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
GCA	giant cell arteritis
IND	Investigational New Drug
IL-6	interleukin-6
ITT	intent-to-treat
IV	intravenous
MRA	magnetic resonance angiography
PBO	placebo
PD	pharmacodynamics
PET-CT	positron emission tomography-computed tomography
PK	pharmacokinetics
PMR	polymyalgia rheumatica
popPK	population pharmacokinetics
QW	weekly
Q2W	every other week
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-36	short-form 36 (questionnaire)
sIL-6R	soluble interleukin-6 receptor

TAB	temporal artery biopsy
TCZ	tocilizumab
wk	week

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 17 November 2016 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, II and III

Extension of indication to include treatment of giant cell arteritis in adult patients for the subcutaneous formulation of RoActemra based on the Phase III study WA28119 (GiACTA). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect information relevant to this indication. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0266/2015) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0266/2015) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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 received Scientific Advice from the CHMP on 16 February 2012. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	17 November 2016
Start of procedure:	24 December 2016
CHMP Rapporteur Assessment Report	17 February 2017
CHMP Co-Rapporteur Assessment Report	27 February 2017
PRAC Rapporteur Assessment Report	24 February 2017
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	2 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	N/A
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 March 2017
Request for supplementary information (RSI)	23 March 2017
CHMP Rapporteur Assessment Report	19 May 2017
PRAC Rapporteur Assessment Report	29 May 2017
Updated PRAC Rapporteur Assessment Report	14 June 2017
PRAC Outcome	9 June 2017
CHMP members comments	12 June 2017
Updated CHMP Rapporteur Assessment Report	14 June 2017
Request for supplementary information (RSI)	22 June 2017
PRAC Rapporteur Assessment Report	5 July 2017
CHMP Rapporteur Assessment Report	5 July 2017
CHMP members comments	10 July 2017
PRAC members comments	10 July 2017
Updated PRAC Rapporteur Assessment Report	13 July 2017
Updated CHMP Rapporteur Assessment Report	13 July 2017
Opinion	20 July 2017

2. Scientific discussion

2.1. Introduction

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 haematopoiesis, 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 signaling. 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.

In the European Union (EU) both pharmaceutical forms of TCZ are approved, in combination with methotrexate (MTX), for the treatment of severe, active and progressive RA, in adults not previously treated with MTX and for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, TCZ can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

The recommended dose for IV administration is 8 mg/kg TCZ every 4 weeks (q4w).

For SC administration, the recommended dose is 162 mg once every week (qw).

The IV formulation of TCZ is also approved in the EU, at the recommended dose, for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Also, RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Background on disease

Giant cell arteritis (GCA or temporal arteritis) is a systemic inflammatory vasculitis of medium- and large-size arteries. The inflammatory process typically involves the extracranial branches of the carotid arteries, but also affects the aorta, aortic arch and its branches. The disease typically occurs in the White population and in individuals older than 50 years of age and was once considered primarily a cranial disease with new onset headaches regarded as the prototypical symptom. However non-cranial manifestations such as polymyalgia rheumatica (PMR) symptoms and limb claudication are other important features. Giant cell arteritis can manifest with ischemic events due to vessel occlusion, most typically central retinal artery occlusion or anterior ischemic optic neuropathy which both lead to irreversible vision loss, and less frequently, subclavian artery occlusion leading to symptomatic ischemic issues affecting the upper extremities. Ischemic events are most frequent early in the disease course and often occur before the initiation of treatment. Less well characterized are the long-term effects of GCA, which include aortic aneurysm.

Glucocorticoids (GC) are the mainstay of treatment for GCA and are typically administered in the form of oral prednisone/prednisolone, although some physicians use pulsed intravenous (IV) glucocorticoids in patients presenting with visual loss. Although glucocorticoids are highly effective at inducing remission of systemic inflammation and preventing acute damage (e.g., blindness), this comes with a high toxicity burden, with approximately 80% of patients suffering GC-related adverse clinical events at 10-year follow-up (Proven et al. 2003). In addition, GC are not as effective at maintaining remission, with many patients (up to 50%) experiencing relapse or flare-up of symptoms during reduction or discontinuation of glucocorticoids (Proven et al. 2003). Other agents, including azathioprine, cyclophosphamide, methotrexate (MTX), infliximab, and etanercept, have shown conflicting or no evidence of benefit in the treatment of GCA. In spite of the paucity of evidence, MTX is used inconsistently as standard of care for glucocorticoid-sparing in relapsing patients. More recently, limited efficacy in the treatment of GCA has been demonstrated with the use of combination treatment with abatacept and prednisone (Langford et al. 2015).

Development aspects

Data to support the efficacy of tocilizumab (also known as RO4877533 and TCZ) in adult patients with giant cell arteritis (GCA or temporal arteritis) are provided from the pivotal Phase III trial (Study WA28119; GiACTA). Study WA28119 was designed to evaluate the efficacy of TCZ plus glucocorticoid treatment compared to treatment with glucocorticoids alone in new-onset and relapsing patients with GCA, as well as to evaluate the safety profile of TCZ treatment in this patient population. The study includes a 52-week blinded period (Part 1) followed by a 104-week open-label period (Part 2), with a total study duration of 156 weeks. Clinical conduct of Part 1 of the study is complete and the primary analysis has been conducted. The Part 2, open-label extension/long-term follow-up, is currently ongoing. The purpose of the open-label extension/long-term follow-up is to describe the long-term safety and maintenance of efficacy after 52 weeks of therapy with TCZ in GCA, to explore the rate of relapse and the requirement for TCZ therapy beyond 52 weeks, and to gain insight into the potential long-term steroid-sparing effect with TCZ.

Additionally, in order to support data from Study WA28119, efficacy data are provided from the publication by Villiger et al. 2016 which describes a Phase II investigator-initiated study (further referred to as Study ML25676 throughout this report) designed to evaluate the efficacy and safety of TCZ + glucocorticoid treatment compared to glucocorticoid treatment alone in the induction and maintenance of disease remission in patients with new-onset and relapsing GCA.

In addition to the safety data derived from the above studies, the safety database is enriched by pooled long-term safety data with IV TCZ in the rheumatoid arthritis (RA) population, referred to as LTE All-exposure RA population.

Scientific Advice was sought from the CHMP.

Communication Type/ Date	Topic	Key Agreements
CHMP Scientific Advice (Feb 2012)	Overall study design	CHMP agreed with the overall study design (incl. the sustained remission endpoint, the inclusion of new-onset and relapsing patients, and the general glucocorticoid tapering schedule.
	Patient selection criteria	CHMP noted that the inclusion criteria into WA28119 differ from the ACR criteria. The planned inclusion criteria allow also a diagnosis by positive imaging. The CHMP expects a validation of the utility of imaging as a diagnostic criterion. Furthermore, it was suggested to have the locally evaluated TAB slides re-read by a central facility since GCA diagnosis takes place before the patients enter the study. **Action taken:** the Sponsor evaluated the possibility to collect the slides from the local laboratories to enable a confirmatory central reading as a quality assessment. However, it was determined that a retrospective collection of the slides was not feasible due to logistical and operational difficulties, in particular because the biopsies were not directly part of the planned assessments during the WA28119 study.
	Definition of "refractory" patients	CHMP noted a lack of clarity whether "refractory disease" referred to patients for whom remission could not be achieved below a certain glucocorticoid dose or whether this included also patients who could not achieve remission at any glucocorticoid dose. **Action taken:** Definition of refractory (relapsing) patients was updated to include those who have active disease despite at least two consecutive weeks of treatment with ≥40 mg/day prednisone (or equivalent) at any time in the amended protocol version 3 (see Table 2).
	Size of safety database	The size of the safety database with 150 TCZ-treated GCA patients was in general considered adequate. However, it was noted that this patient population was older than RA patients and could thus be more vulnerable and may have an increased risk of infections. **Action taken:** The submission dossier contains analyses of safety of TCZ in RA patients as well as analyses of real world data in GCA patients not treated with TCZ to determine the background rates for relevant safety parameters.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study No. (Phase)	Study Design,	Population	No. of Patients	Dose, Route, and Regimen
Pivotal Phase III Study				
WA28119 (Phase III)	Multicenter, randomized, double-blind placebo-controlled superiority study to assess the efficacy and safety of TCZ in patients with GCA Part 1: 52-week blinded period for primary analysis Part 2: 104-week open-label extension to assess maintenance of disease remission and long-term safety in patients with newly diagnosed or relapsing GCA.	Patients ≥ 50 years with new-onset GCA and with relapsing GCA	251[a] (149 receiving TCZ)	162 mg SC TCZ (QW) + 26-week prednisone taper regimen 162 mg SC TCZ (Q2W) + 26-week prednisone taper regimen SC placebo + 26-week prednisone taper regimen SC placebo + 52-week prednisone taper regimen
Supporting Study				
ML25676 (Phase II)	Single-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of TCZ in the induction and maintenance of disease remission in patients with newly diagnosed or relapsing GCA	Patients ≥ 50 years with new-onset GCA and with relapsing GCA satisfying 1990 ACR criteria	30 (20 receiving TCZ)	8 mg/kg IV TCZ (13 infusions given in 4 week intervals until Week 52) + oral prednisolone (starting at 1 mg/kg per day) taper regimen IV placebo (13 infusions given in 4 week intervals until Week 52) + oral prednisolone (starting at 1 mg/kg per day) taper regimen

ACR: American College of Rheumatology; GC: glucocorticoids; GCA: Giant Cell Arteritis; IV: intravenous; QW: weekly; Q2W: every other week; SC: subcutaneous; TCZ: tocilizumab

[a] Of the 251 randomized patients, 1 patient who was randomized to the TCZ Q2W group withdrew the same day they were randomized, and did not receive any study treatment. This patient was excluded from the ITT population

Study WA28119 includes a 52-week blinded period (Part 1) followed by a 104-week open-label period (Part 2), with a total study duration of 156 weeks. Clinical conduct of Part 1 of the study is complete and the primary analysis has been conducted. At the time of the Part 1 clinical cut-off date, 11 April 2016, 88 patients had at least 100 weeks of follow up in Part 2 of the study.

2.3.2. Pharmacokinetics

GCA study and Concentration-time-profile

The PK/PD behaviour of TCZ has been previously characterized extensively in various populations, most notably in patients with rheumatoid arthritis (RA).

PK and PD data for this new patient population derives mainly from a single Phase III clinical study of TCZ administered SC to Giant Cell Arteritis (GCA) patients (WA28119).

Phase III Study in GCA Patients				
Protocol	**Study Design**	**Patient Population**	**Dose, Route, Regimen**	**Number of Patients**
WA28119	Multicenter, randomized, double-blind placebo-controlled parallel group superiority study to assess the efficacy and safety of TCZ in patients with GCA Part 1: 52-week blinded period for primary analysis Part 2: 104-week open-label extension to assess maintenance of disease remission in patients with GCA.	Patients ≥ 50 years with new-onset GCA and with relapsing GCA	162 mg SC TCZ (QW) + 26-week prednisone taper regimen 162 mg SC TCZ (Q2W) + 26-week prednisone taper regimen SC placebo + 26-week prednisone taper regimen SC placebo + 52-week prednisone taper regimen	251 (149 receiving TCZ)

GCA = Giant Cell Arteritis; QW = weekly; Q2W = every 2 weeks; SC = subcutaneous; TCZ = tocilizumab

Only data from Part 1 of the study is presented. Part 2 of the study is currently ongoing and will be presented separately. The final CSR will be submitted in Q1 2019.

Comparisons were made between the two dosing regimens and to findings in the RA population. Additionally, a population pharmacokinetics analysis was performed to describe the PK characteristics of TCZ in patients with GCA following multiple SC administrations of TCZ and to investigate the potential effect of selected covariates on the PK parameters.

Study WA28119 – PK results

A secondary objective of the study was to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in combination with a 26-week prednisone taper regimen in patients with GCA. During the 52-week double-blind period of the study (Part 1), study drug (TCZ or placebo) was supplied in 1-mL, ready-to-use, single-use PFS, each delivering either 162 mg (0.9 mL) of TCZ solution or matching placebo (SC administration).

For assessment of serum TCZ concentrations, IL-6, and sIL-6R levels, pre-dose samples were collected in all patients at Weeks 0, 1, 2, 3, 8, 16, 24, 36, 48, and 52. A sample was also drawn at early withdrawal and Week 8 follow-up (except IL-6).

In addition, approximately 35 patients participated in a pharmacokinetic substudy. In these patients, additional PK samples for assessment of serum TCZ concentrations were drawn at 24, 48, 72 96, and 120 or 144 hours following the first dose and following dose at Week 16, and pre-dose at Weeks 17 and 18.

Table 1 - Schedule of Assessments for Pharmacokinetic Substudy

Day (±0 days)	Baseline						Wk 1	Wk 2	Wk 16						Wk 17	Wk 18
	0	1	2	3	4	5 or 6 [a]	7	14	112	113	114	115	116	117 or 118 [a]	119	126
SC injection [b]	x						x	x	x						x	x
Predose	x [c,d]						x [c,d]	x [c,d]	x [c,d]						x [d]	x [d]
24 ± 2 hr		x								x						
48 ± 2 hr			x								x					
72 ± 2 hr				X								x				
96 ± 2 hr					x								x			
120 ± 2 hr or 144 ± 2 hr [a]						x								x		

PK = pharmacokinetic; SC = subcutaneous; TCZ = tocilizumab; Wk = Week.

Note: All samples will be obtained according to the procedures in the Sample Handling and Logistics Manual for analysis of TCZ.

[a] Patients should be encouraged to provide PK samples on either Day 5 or 6 of the week for baseline assessments and either Day 117 or 118 for Week 16 assessments. If the patient is not available on either day, this will not be considered a protocol deviation.

[b] Patients will receive SC injections at baseline and Weeks 1, 2, 16, 17, and 18 in the clinic to ensure the dosing time is recorded accurately.

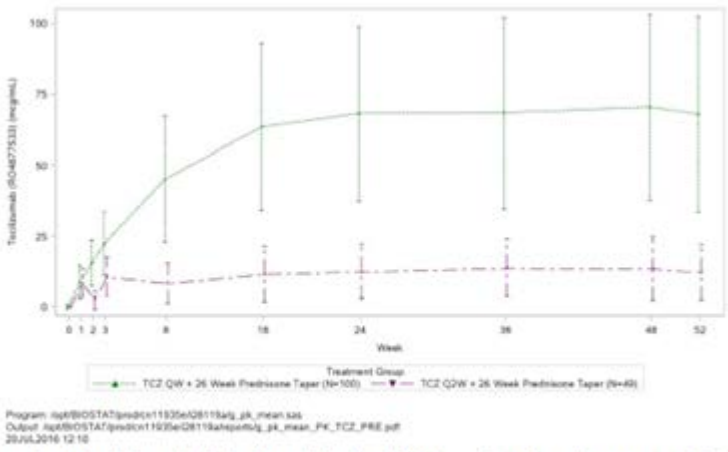
[c] These are the same samples obtained from all patients in Appendix 1. No duplicate samples for patients participating in the PK substudy are necessary.

[d] The PK sample should be collected prior to the TCZ administration at baseline and at Weeks 1, 2, 16, 17, and 18. Patients must not inject TCZ at home before PK sample collection at the site.

In total, the data set comprised 1263 serum TCZ concentrations from a total of 149 GCA patients treated with TCZ. Patients were treated with placebo or TCZ 162 mg, QW or Q2W SC for 52 weeks.

Mean pre-dose TCZ concentrations increased with repeated dosing from baseline to Week 16 and appeared to reach steady state thereafter (Figure below). An approximate 6-fold and 2-fold accumulation in mean TCZ Ctrough at steady state was observed for patients in the QW and Q2W groups, respectively. Based on observed data for all patients, the steady-state Ctrough values were 67.93±34.40 µg/mL and 12.22±10.02 µg/mL in the SC QW group and Q2W group, respectively. The large increase in exposure between QW dosing and Q2W dosing is consistent with the known effect of concentration-dependent elimination of TCZ. The nonlinear elimination pathway of TCZ is believed to represent a target-mediated clearance process due to the binding to soluble and membrane bound IL-6R receptors.

Figure 1 - Study WA28119: Mean ± SD Serum TCZ Concentrations by Visit (TCZ QW vs Q2W)

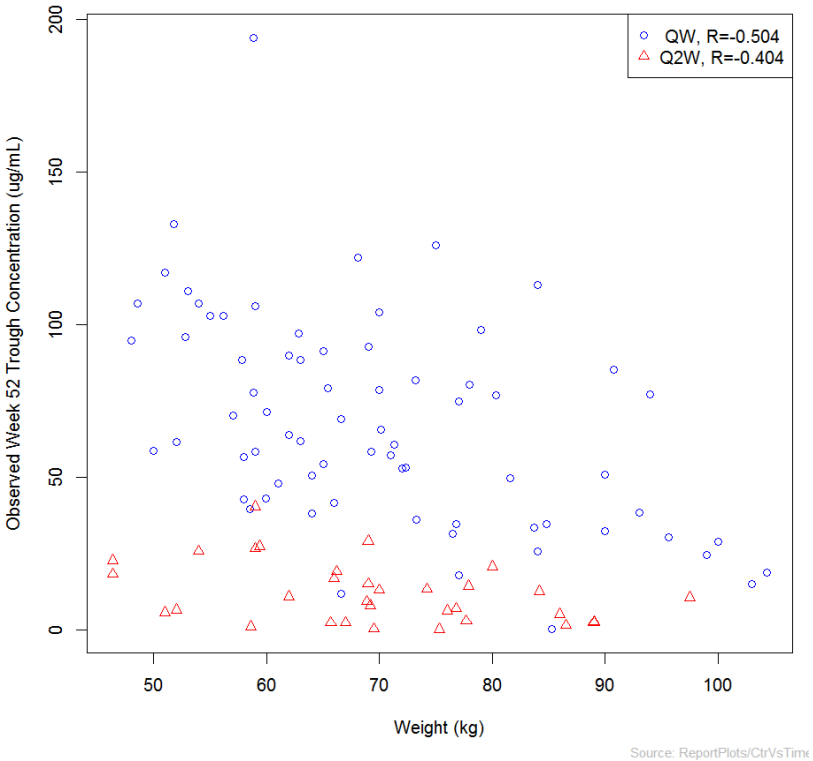


Note: Pre-dose below the limit of quantification (BLQ) records at Baseline are set to 0; all other BLQ records are set to missing

Study Population

Mean (range) weight and body surface area of the patients in this study was 70.3 kg (46.4 to 124 kg) and 1.76 m2 (1.34 to 2.25 m2), respectively. Mean (range) age was 69.4 years (51 to 91 years). The dataset contained the data from 37 (24.8%) male and 112 (75.2%) female patients; 100 (67.1%) patients received TCZ QW doses and 49 (32.9%) of patients received TCZ Q2W doses. The majority of patients were Caucasians (96.0%) and non-Hispanic (94.6%). Most of the doses (76.8%) were injected to the abdominal wall, with 19.2% of doses injected to the thigh, and 4% injected to the arm.

To assess whether there was an exposure body-weight effect, a scatter plot of observed Ctrough at Week 52 versus body weight was displayed resulting from study WA28119:



There was a positive trend for higher exposure in patients with lower body weight. The associated Pearson's correlation coefficient (R) was −0.504 and -0.404 for the QW and Q2W regimens, respectively, which indicates a moderate inverse correlation between Ctrough and body weight.

The relationship between exposure and body weight as well as other body size parameters (such as body surface area) following SC administration of TCZ is discussed further in the popPK results.

To evaluate whether there was a difference in exposure between responders versus non-responders, the average Ctrough at Week 52 was compared: In the TCZ QW group, the mean±SD TCZ concentrations at Week 52 in responders vs. non-responders were 69.2±35 µg/mL and 64.9±33.5 µg/mL, respectively. In the TCZ Q2W group, the mean ± SD TCZ concentrations were 13.3±10.4 µg/mL and 9.0±8.4 µg/mL, respectively. There was a slight but consistent trend, notably in the Q2W regimen, toward higher Ctrough values in responders compared with non-responders; however, the differences were small considering the variability in the data.

2.3.3. Pharmacodynamics

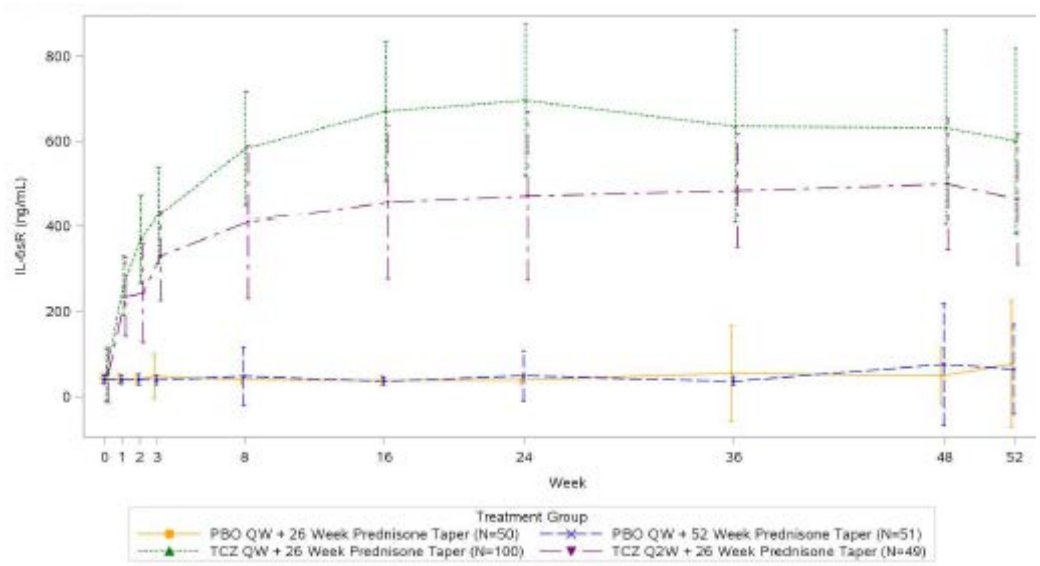
The PD of TCZ was characterized by assessing two mechanistic markers of activity: soluble interleukin-6 receptor (sIL-6R) and interleukin-6 (IL6) levels and two markers of inflammation: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

The time course of markers of TCZ mechanism-related activity (IL-6 and sIL-6R) and PD markers of inflammation (CRP and ESR) were not statistically different between the two treatment groups. However, there was a trend for a slightly higher increase (sIL-6R) or reductions (IL-6) in the PD parameters following QW regimen, consistent with higher Ctrough. CRP and ESR levels in both TCZ groups were markedly reduced relative to placebo with no notable difference between the dosed groups.

sIL-6R

The profiles of pre-dose serum sIL-6R concentrations over nominal time are displayed in the Figure below:

Figure 2 - Mean ± SD soluble IL-6R Levels by Visit (TCZ QW, Q2W, PBO + 26 Week, PBO + 52 Week - Study WA28119)



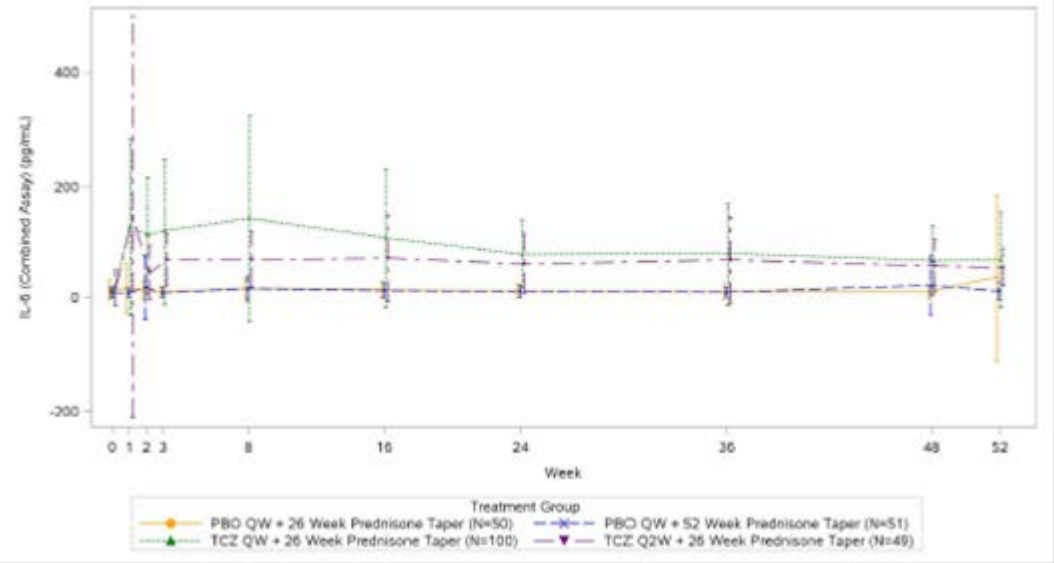
Levels of sIL-6R steadily increased after the first dose, reaching a plateau around Week 16. At Week 52, the sIL-6R levels (mean ± SD) were higher by 29% in the TCZ QW group (600.5±217.5 ng/mL) as compared to the TCZ Q2W group (464.3±153.6 ng/mL). The sIL-6R responses to TCZ treatment in both regimens are comparable to the mean levels in RA patients at steady state (Week 24) who received the same dose regimens (599±180.1 ng/mL for TCZ QW in study WA22762 and 449±217.8 ng/mL for TCZ Q2W in study NA25220). Levels of sIL-6R in the placebo groups during the 52 weeks of study essentially remained unchanged from baseline.

IL-6

The mean ± SD pre-dose levels of IL-6 increased rapidly to 125.86±158.64 pg/mL one week after the first dose in the TCZ QW group, and subsequently plateaued to 65.99±84.92 pg/mL by Week 52 (Figure below). Similarly, the mean IL-6 levels in the TCZ Q2W group increased rapidly one week after the first dose (142.72±356.67 pg/mL), and then decreased to 42.62±47.87 pg/mL at Week 2, corresponding with decreased TCZ concentration at the end of the first dosing interval. Mean IL-6 levels in TCA Q2W group subsequently increased to 66.20±47.11 pg/mL at Week 3 and plateaued out until Week 52 (52.70±33.10 pg/mL). At Week 52, the IL-6 levels were higher (25%) in the TCZ QW group compared to the TCZ Q2W

group. Levels of IL-6 in the placebo groups during the 52 weeks of study essentially remained unchanged from baseline.

Figure 3 - Mean ± SD IL-6 Concentrations by Visit (TCZ QW, Q2W, PBO + 26 Week, PBO + 52 Week - Study WA28119)



The mean values of CRP and ESR (see Figures below) decreased rapidly in both the TCZ QW and TCZ Q2W groups, and remained low throughout the study.

Mean ± SD levels of CRP at Week 52 were 1.42±4.30 and 0.83±1.60 mg/L for the QW and Q2W regimens, respectively. Mean ± SD levels of ESR at Week 52 were 4.84±4.04 and 7.06±6.79 mm/h for the QW and Q2W regimens, respectively. CRP and ESR levels at baseline for all patients were close to the upper end of the normal range (8 mg/L) in healthy individuals. This is in contrast to the baseline acute phase reactants observed in RA patients, in which the majority had elevated CRP and ESR at baseline, and could be due to the fact that the GCA patients were already receiving high dose glucocorticoids at study entry, which suppresses the acute phase reactants. During the 52 weeks of study, the mean CRP and ESR levels in the placebo groups essentially remained unchanged relative to their baseline levels.

Figure 4 - Mean ± SD CRP Levels by Visit (TCZ QW, Q2W, PBO + 26 Week, PBO + 52 Week - Study WA28119)

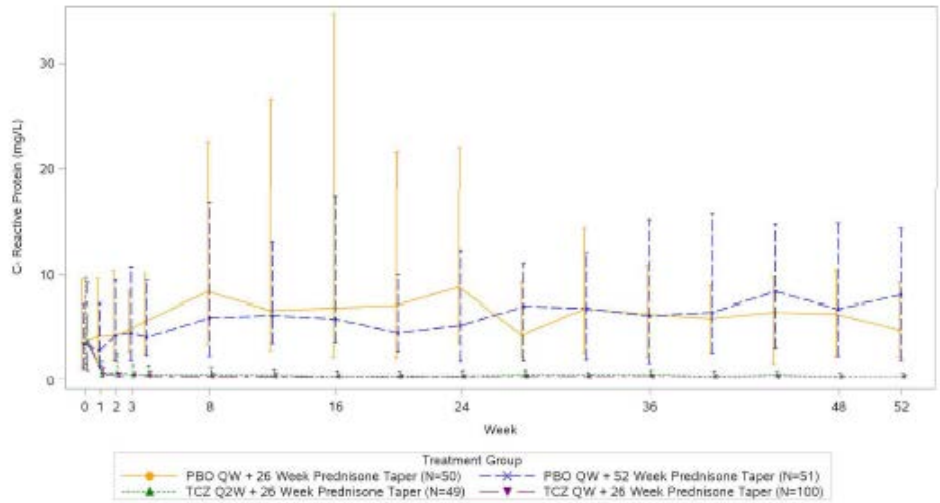
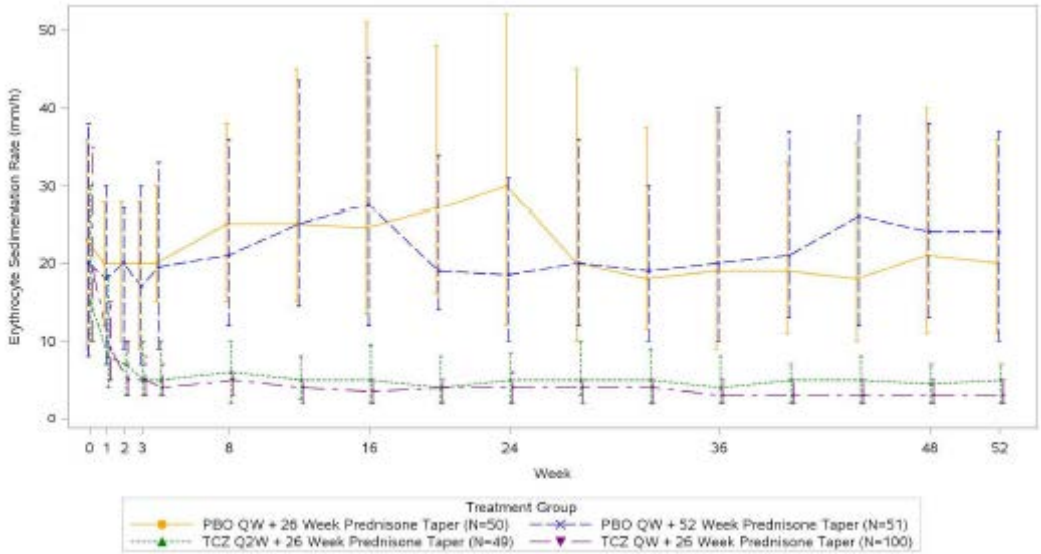


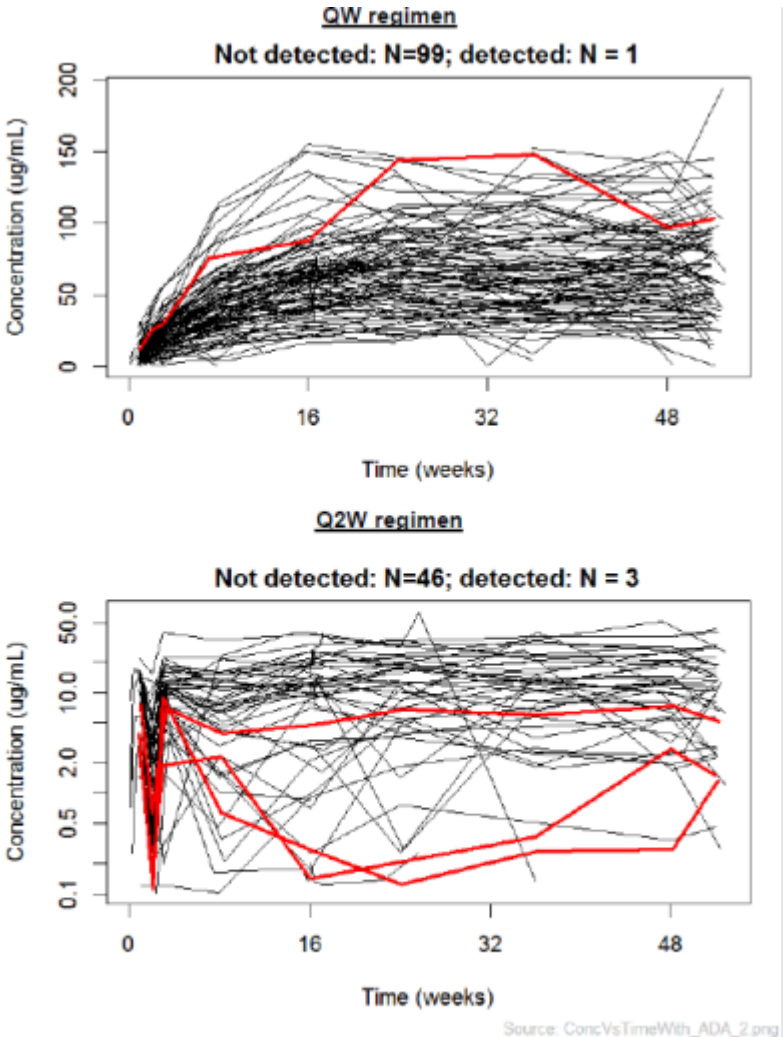
Figure 5 - Mean ± SD ESR Levels by Visit (TCZ QW, Q2W, PBO + 26 Week, PBO + 52 Week - Study WA28119)



Immunogenicity results

Pre-dose TCZ concentrations were evaluated for the 4 patients who were negative for ADAs at baseline but developed positive post-baseline anti-TCZ antibodies following initiation of treatment: 1 in the TCZ QW (1.1%) and 3 in the TCZ Q2W (6.5%) group. All ADAs were transient, and each occurred only at a single time point over the 52 week dosing period. As shown in the Figure below, patient 10221 in the QW group and patient 10862 in the Q2W group did not show any trend for decreased TCZ concentration at Week 24 and 32 when their ADA test showed positive results and concentrations were similar to or at the high end of observed values among all patients on this regimen. In contrast, patients 10227 and 10628 (both in the TCZ Q2W group) showed a transient decrease at Week 24 when their ADA test showed positive results and had observed concentration-time courses which were in the lower range of all exposures in the group. None of the patients, who developed treatment-induced ADA, experienced any anaphylaxis, serious and/or clinically significant hypersensitivity reactions, injection site reactions, or withdrew due to lack of efficacy.

Figure 6 - Individual Observed Serum TCZ Concentration Profiles for Patients with Treatment Induced anti-TCZ Antibodies (Study WA28119)



Source: ConcVsTimeWith_ADA_2.png

Note: Observed TCZ concentrations over time of patients that did (thick, red) or did not (thin, black) have ADA detected.

Note: Pre-dose BLQ records at Baseline are set to 0; all other BLQ records are set to missing

2.3.4. PK/PD modelling

Population PK Modelling and Analysis

The data set comprised 1263 serum TCZ concentrations from a total of 149 GCA patients treated with TCZ over 52 weeks. Patients were treated with placebo or TCZ 162 mg, QW or Q2W SC for 52 weeks.

A two-compartment PK model with first-order absorption (following SC administration) and parallel linear and Michaelis-Menten (non-linear) eliminations was previously developed for adult RA patients (Model 317). The compartmental models were parameterized in terms of CL(s) and volume(s) of distribution, Q, Vp, Vmax, the Michaelis-Menten constant (KM), Ka, and Fsc. Fsc was fixed to the value obtained from adult RA patients, since there was no IV data available for GCA patients. Inter-subject variability was incorporated on linear CL, Q, Vc, Vp, and Ka.

The final population PK parameter estimates for GCA patients (Model 107) and predicted covariate effects are listed in the Tables below. All structural and covariate effect parameters were estimated precisely (RSE 5% - 22%). The RSE values of the random effect variance parameters were in the range of 17% - 27%, with the exception of the random effect on the peripheral volume that was poorly estimated.

Shrinkage of the random effects was low to moderate (2% - 27%) with the exception of the random effect on the peripheral volume (with shrinkage of 48.9%).

Table 2 - Final population PK parameter estimates for GCA patients (Model 107) and predicted covariate effects

Parameter		Estimate	%RSE	95%CI
CL(L/day)	θ_1	0.16	4.58	0.146 - 0.174
V_c (L)	θ_2	4.09	11.6	3.16 - 5.01
Q (L/day)	θ_3	0.245	22.2	0.138 - 0.352
V_p (L)	θ_4	3.37	15.2	2.37 - 4.38
V_{max} (µg/mL/day)	θ_5	1.9	9.83	1.54 - 2.27
K_M (µg/mL)	θ_6	0.705	22.1	0.399 - 1.01
K_a (1/day)	θ_7	0.193	10.7	0.152 - 0.233
F_{sc}	θ_8	0.795	Fixed	
$CL_{WT} = Q_{WT}$	θ_9	1.14	13.9	0.83 - 1.45
$V_{c,WT} = V_{p,WT}$	θ_{10}	0.666	20.5	0.398 - 0.933
$K_{a,\ age}$	θ_{11}	-0.442	Fixed	
$F_{sc,injection\ to\ thigh}$	θ_{12}	1.11	2.67	1.06 - 1.17

Parameter		Estimate	%RSE	95%CI	Variability %	Shrinkage %
ω^2_{CL}	$\Omega(1,1)$	0.0561	26.7	0.0267 - 0.0854	CV=23.7	27.1
ω^2_{V2}	$\Omega(2,2)$	0.0822	18.6	0.0522 - 0.112	CV=28.7	10.0
ω^2_{V3}	$\Omega(3,3)$	0.227	63.5	0 - 0.508	CV=47.6	48.9
ω^2_{ka}	$\Omega(4,4)$	0.174	22.3	0.0982 - 0.251	CV=41.8	25.6
ω^2_{EPS}	$\Omega(5,5)$	0.129	16.7	0.0871 - 0.172	CV=36.0	1.9
σ^2	$\Sigma(1,1)$	1	Fixed			4.8
σ_L	θ_{13}	1.41	25.2	0.711 - 2.10		
σ_H	θ_{14}	0.133	7.59	0.114 - 0.153		
σ_{50} (µg/mL)	θ_{15}	1.58	37.0	0.433 - 2.73		

CI = confidence interval; CL = clearance; CV = coefficient of variation (CV = 100*SD%); F_{sc} = subcutaneous bioavailability; K_M = Michaelis-Menten constant, K_a = absorption rate; Q = inter-compartmental clearance; RSE = relative standard error (%RSE = 100*SE/PE, where SE is standard error and PE is a parameter estimate); SD = standard deviation; Vc = central volume of distribution; Vp = peripheral volume of distribution; Vmax = maximum elimination rate; WT = weight, θ = fixed effect parameter, Ω = inter-individual covariance matrix, ω = inter-individual variance, σ = standard error

Parameter	Covariate	Reference Value	Covariate Value[a]	Covariate Effect Value [95%CI] (%)
CL	Body weight	70 kg	48.6 kg	-34.0 [-41.1; -26.1]
			102 kg	53.6 [36.7; 72.7]
V_c, V_p	Body weight	70 kg	48.6 kg	-21.6 [-28.9; -13.5]
			102 kg	28.5 [16.2; 42.1]
K_a	Age	50 years	53.7 years	-3.1 [fixed]
			84 years	-20.5 [fixed]
F_{sc}	Injection site	Arm, abdomen	Thigh	11.5 [5.6; 17.3]

CL = clearance; F_{sc} = bioavailability; K_a = absorption rate; V_c = central volume of distribution; V_p = peripheral volume of distribution

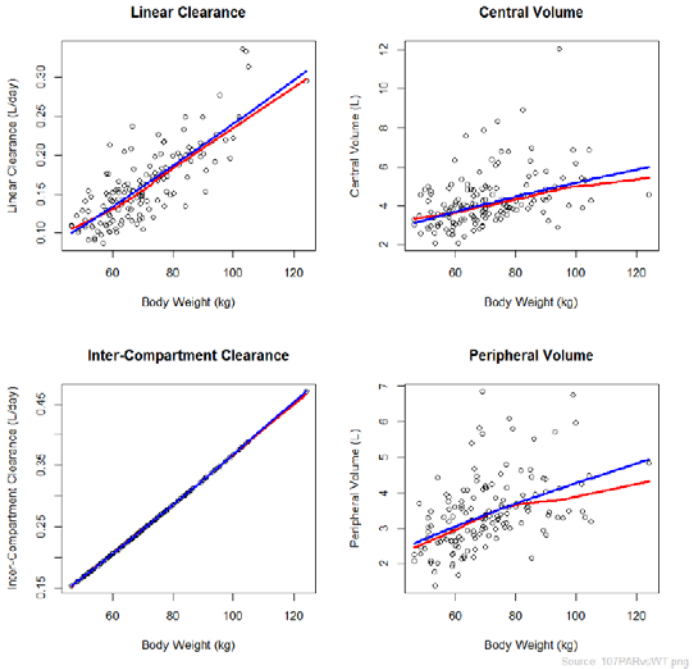
[a] The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis data set.

Based on prior knowledge from the previous population PK analysis for adult RA patients, the population PK model contained the following covariates: body weight on linear CL, inter-compartmental CL (Q), and volume of distribution of the central (Vc) and peripheral (Vp) compartments; age on absorption rate constant (Ka); thigh injection site on SC bioavailability (Fsc); HDL on CL; serum albumin and total protein on Vc and Vp; and creatinine CL on maximum elimination rate (Vmax). This model was the starting point of the analysis. The model was evaluated and refined using the data collected from GCA patients (Study WA28119).

The significant covariates identified for GCA patients were: body weight on linear CL, Q, Vc, and Vp; age on Ka, and injection in the thigh on Fsc. The data set included relatively narrow range of ages (51 to 91 years), which leads to a high relative standard error estimated for the age effect on Ka. Therefore, age effect on Ka was fixed to be equal to the value in the adult RA model.
Other covariates previously identified for adult RA patients were: HDL on CL; serum albumin and total protein on Vc and Vp, and creatinine CL on Vmax. These covariates were tested in the current model for GCA patients; none of them were significant, and they were removed from the model. Additionally, the presence of ADA was not found to influence the PK of TCZ.

Body weight is the main covariate which has an appreciable impact on the PK of TCZ, and the relationships of the individual PK parameters with body weight are shown in the Figure below.

Figure 7 - Relationships of the individual PK parameters with body weight



Note: Individual estimates are plotted versus individual body weight. A lowess smoothing line and the line that illustrates dependence on weight estimated by the model are shown for comparison. **Blue line**: dependence on weight estimated by the final model; **Red line**: lowess smoothing line

Note: Pre-dose BLQ records at Baseline are set to 0; all other BLQ records are set to missing

Renal impairment is not anticipated to impact the PK of TCZ and as anticipated creatinine CL was not identified as a significant covariate in the model. Based on the slightly older population with this disease one-third of the patients in the trial had moderate renal impairment; no significant impact on TCZ exposure was noted in these patients.

Covariate effects identified in adult RA patients were reevaluated and non-significant effects were removed. Additional covariate effects were tested and discarded as they did not improve the fit. Distributions of the random effects for patients with and without detected ADAs were compared and the effects of ADAs were tested as time-dependent covariates on linear and Michaelis- Menten clearances.

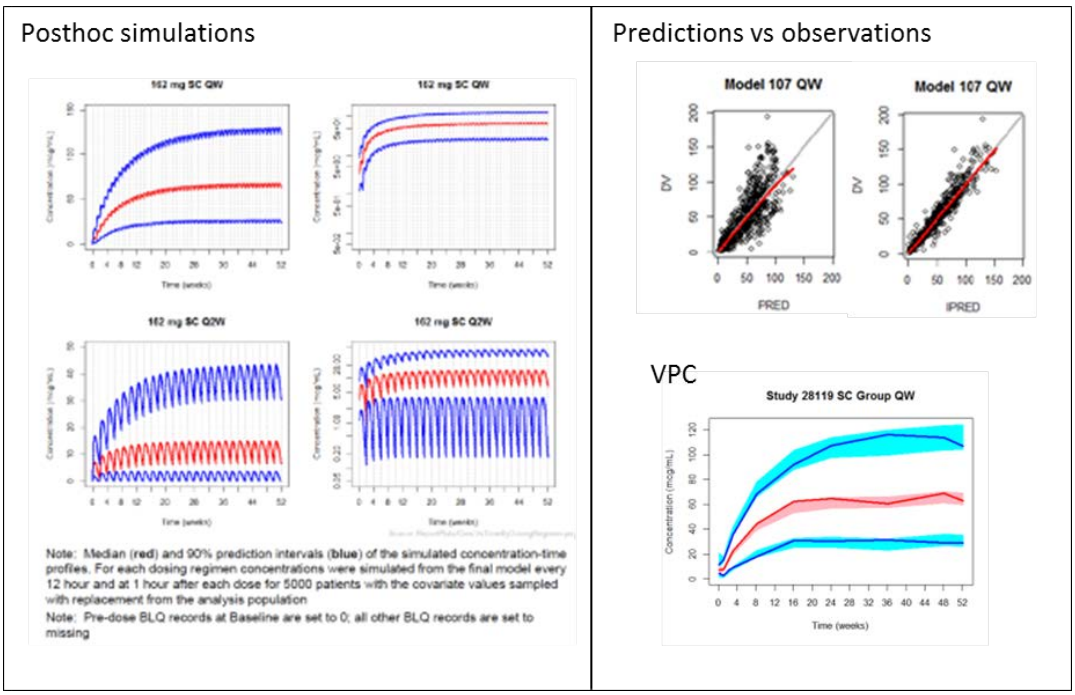
Predicted individual exposure parameters at steady-state are summarized in the Table below. Steady-state Cmean value for the QW regimen (71.3 µg/mL) was about 4.4 times higher than for the Q2W regimen (16.2 µg/mL), Cmax value for the QW regimen (73.0 µg/mL) were 3.8 times higher than for the Q2W regimen (19.3 µg/mL), while Ctrough values for the QW regimen (68.1 µg/mL) was 6.1 times higher than for the Q2W regimen (11.1 µg/mL).

Table 3 – Summary of Predicted Individual Steady-State Exposure Parameters by Dosing Regimen

Dose Regimen	N	AUCτ (µg/mL*day)	C_{mean} (µg/mL)	C_{max} (µg/mL)	T_{max} (day)	C_{trough} (µg/mL)
Mean (SD)						
TCZ 162 mg QW	100	499.2 (210.4)	71.3 (30.1)	73 (30.4)	3 (0.1)	68.1 (29.5)
TCZ 162 mg Q2W	49	227.2 (165.4)	16.2 (11.8)	19.3 (12.8)	4.7 (0.6)	11.1 (10.3)
Median [range]						
TCZ 162 mg QW	100	494.5 [82-1041.5]	70.6 [11.7-148.8]	72.1 [12.2-151]	3 [2.5-3]	67.2 [10.7-144.5]
TCZ 162 mg Q2W	49	191.3 [7.7-685.9]	13.7 [0.5-49]	17.2 [1.1-56.2]	4.5 [2.5-6]	7.7 [0.1-37.3]

N = number of patients; QW = every week; Q2W = every 2 weeks; SC = subcutaneous; TCZ = tocilizumab

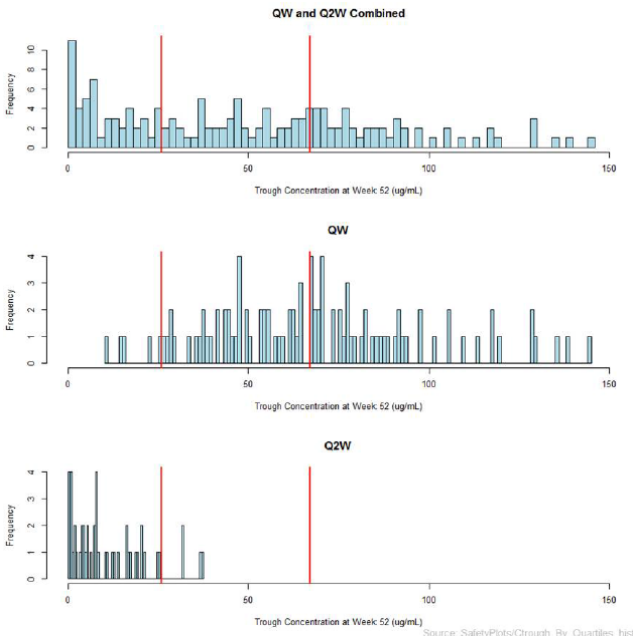
Visualization showed comparable mean concentration time profiles over 52 weeks compared to the observed values.



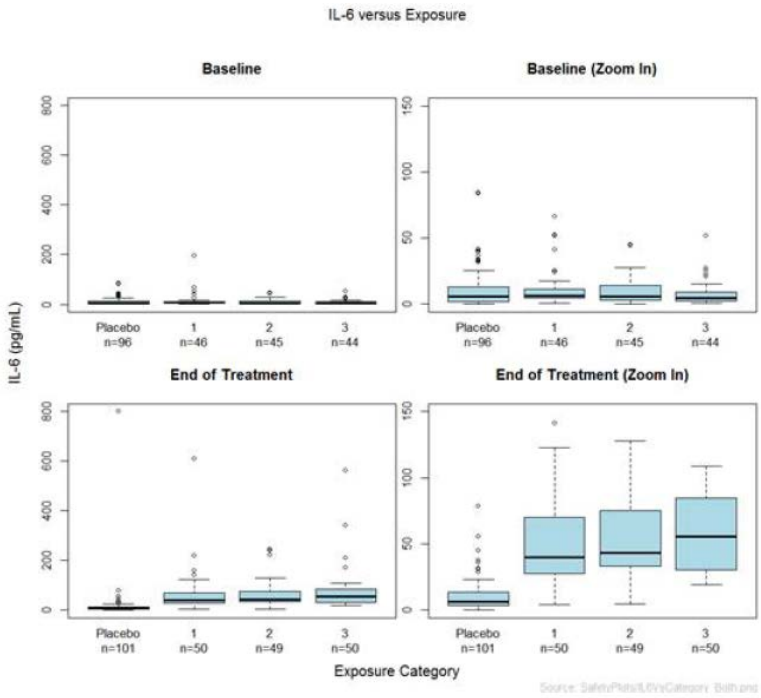
Exposure efficacy analysis

Exposure-efficacy relationship of TCZ in GCA patients was described by exposure tertiles (week 52) and graphical analyses for PD and efficacy marker sIL-6R, CRP, and ESR as well for some secondary and exploratory efficacy endpoints (cumulative glucocorticoid dose and annualized relapse rate up to Week 52). The distribution of Ctrough values reached by week 52 is depicted in the Figure below.

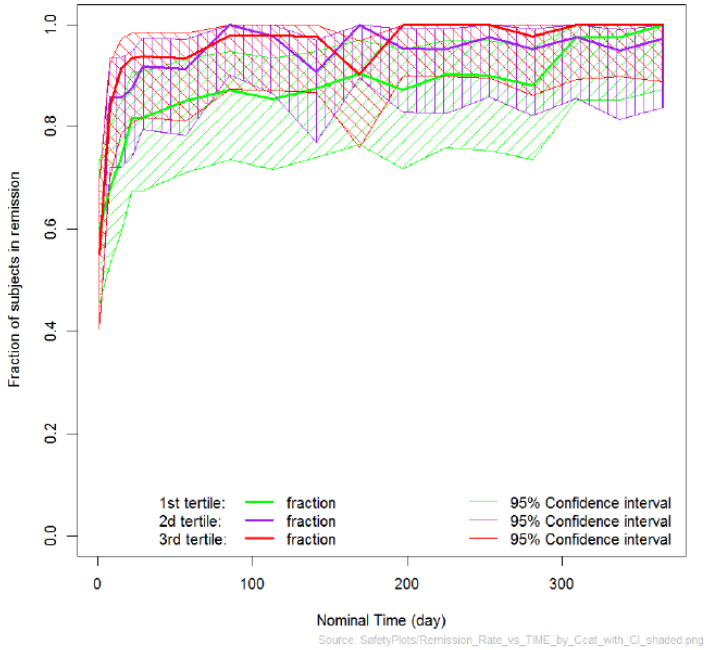
Figure 8 - Distribution of Ctrough values reached by week 52



sIL-6R levels increased with time and with increasing exposure; CRP and ESR decreased with time and with increasing exposure and remained at low levels in all exposure categories; the biggest difference in the PD markers noted between the 1st tertile and upper two tertiles; the between-subject variability observed in sIL-6R, CRP and ESR levels decreased slightly with increasing exposure.

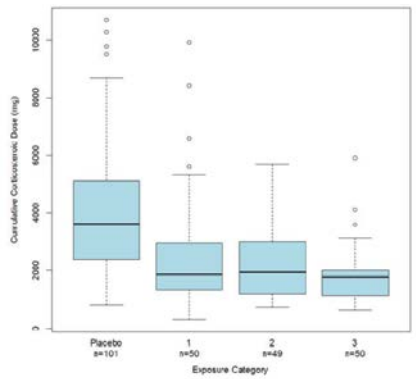


Tertile analysis showed that primary efficacy endpoints (sustained remission up to Week 52) were similar in all TCZ exposure categories with a small, but not statistically significant trend of increasing efficacy with exposure.



Tertile analysis regarding secondary and exploratory efficacy endpoints (cumulative glucocorticoid dose and annualized relapse rate up to Week 52) showed overall similarity in all TCZ exposure categories.

Cumulative Glucocorticoid Dose versus Exposure Category



Annualized relapse rates:

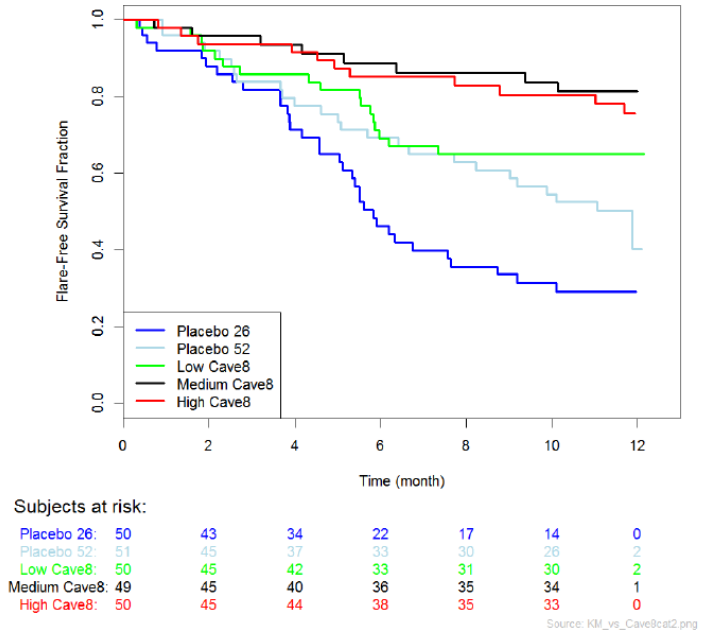
Exposure (tertile of $C_{trough52}$)	N	Annualized Number of Flares	
		Mean (Standard Deviation)	Median [Range]
Placebo	101	1.5 (2.0)	1.0 [0.0-12.6]
Low (1st tertile)	50	0.7 (1.1)	0.0 [0.0-4.0]
Medium (2nd tertile)	49	0.4 (0.7)	0.0 [0.0-2.0]
High (3rd tertile)	50	0.3 (0.8)	0.0 [0.0-4.0]

To characterize the relationship between TCZ exposure and time to first flare in patients with GCA a Cox proportional-hazards regression model was used. The following covariates were included in the analysis: demography (body weight, age, gender, smoking status [yes, no]), baseline disease status [new onset, relapsed] and TCZ exposure (treatment effect [TCZ, placebo], Cave8). The individual predicted average concentration up to Week 8 from treatment start (Cave8) was used as a surrogate for exposure.

A nonlinear Emax model was applied to characterize the effect of concentration (Cave8). The Cox proportional-hazards analysis identified TCZ exposure and gender as the only two covariates which were significant predictors for the risk of flare.

Risk of flare for males was ~3 times lower compared to females (HR = 0.320). The reference for the effect of TCZ exposure is Cave8=3.346 µg/mL (=EC50 value).

Figure 9 - Kaplan-Meier Plot of Time to First Flare by Exposure (Tertile of Cave8)



Note: **1st tertile** = C_{ave8}: 0.50–14.0 µg/mL; **2nd tertile** = C_{ave8}: 14.3–29.1 µg/mL; **3rd tertile**: C_{ave8}: 29.1–69.9 µg/mL

Results showed that patients in the QW group achieved a range of exposures which provided the maximal possible benefit. Patients in the 1st tertile in the Q2W group were at a higher risk for an earlier time to flare. Gender was also identified as a statistically significant predictor for the risk of flare with females identified as being at a higher risk. This finding may be influenced by the fact that 75% of the study participants were female due to a higher prevalence of GCA in females. No other prognostic factors had a significant effect on the risk of flare in GCA patients.

Model	Covariate	B	SE	RSE	HR	HR95CI	OFV	BIC
$C_{ave8}/(EC_{50}+C_{ave8})$ + SEX + $Plac_{52}$	$C_{ave8}/(EC_{50}+C_{ave8})$, EC_{50}= 3.346 µg/mL	-1.826	0.2975	16.3	0.1611	0.08993-0.2886	936.54	958.62
	SEX = 1	-1.141	0.311	27.26	0.3196	0.1737-0.5878		
	Placebo 52	-0.6304	0.2628	41.69	0.5324	0.3181-0.8911		

β: estimate of the coefficient on a model parameter; BIC: Bayesian Information Criteria computed as OFV+p×log(n), where n=250 (log(n)=5.52) is the number of observations and p is the number of model parameters; HR = hazard ratio computed as exp(β); HR95%CI = 95% confidence intervals on hazard ratio; OFV: objective function value; RSE = relative standard error of β estimate (%); SE = standard error of β estimate

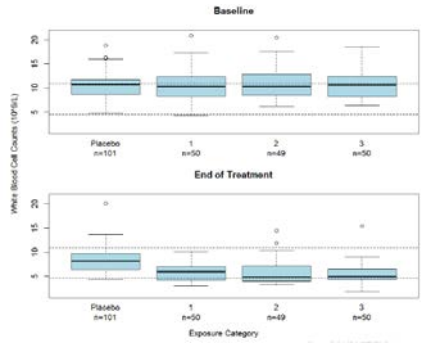
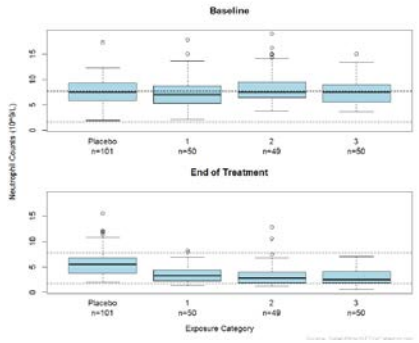
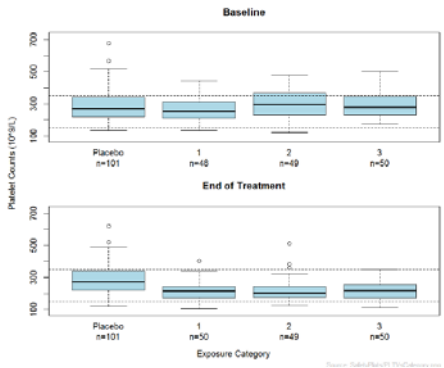
Exposure safety analysis

Graphical analyses to describe the exposure-safety relationships for SC administration of TCZ in patients with GCA were provided.

Consistent with the previous body of data in RA, there was no apparent association of TCZ concentrations or exposure with the occurrence of any SAEs, or AEs in system organ class (SOC) “Infections and Infestations” or SOC "Gastrointestinal disorders".

The only detected signal was a slightly higher percentage of Grade 3+ AEs in the QW treatment arm (14%, 9%, and 2% for SAEs, II AEs, and GI AEs respectively versus 8.2%, 6.1%, and 0% for the respective AEs in the Q2W treatment arm), but the number of events were too low to make any conclusions.

There was a trend of greater decline of hematology parameters (white blood cells, neutrophils, and platelets) with increasing exposure, which reached a plateau at higher exposure levels for white blood cell and neutrophil counts.

White blood cells	Neutrophils	Platelets
		

There was no association of TCZ concentrations with the occurrence of neutropenia or thrombocytopenia.

The following safety laboratory parameters were investigated: white blood cell counts, neutrophil counts, platelet counts, total bilirubin, ALT, AST, serum albumin, total protein, total cholesterol, and LDL cholesterol. Platelet counts time course was similar for all tertiles. Most biochemistry parameters (total bilirubin, ALT, AST, total protein, and total cholesterol) did not change during treatment. Small increases in serum albumin and LDL-cholesterol in the TCZ treatment groups were not associated with exposure. The increase in serum albumin over time was not dependent on TCZ exposure, and the albumin levels stayed below the upper limit of normal value for all exposure categories. Slight increases of LDL-cholesterol in the TCZ treatment groups appeared to have some dependence on TCZ exposure. However an examination of median changes from baseline (increase) in the three tertiles (0.27, 0.68 and 0.445 mg/dL, respectively) did not support this.

2.3.5. Discussion on clinical pharmacology

PK and PD of TCZ in GCA patients were assessed based on Part 1 of Phase III Study WA28119. 149 patients received 162 mg of TCZ SC QW (N=100) or Q2W (N=49). Limited information on Part 2 of Study WA28119 is included in the submission; the final report is awaited and will be provided by Q1 2019. A phase II study (ML25676) was conducted where TCZ has been administered intravenously. Results will be provided for further analyses regarding PK characterization and comparison with RA patients. Analyses integrating IV PK results should in particular focus on a more precise description of clearance and bioavailability.

Comparison of PK and PD outcomes in the GCA population relative to RA

Data from both RA and GCA populations were fitted using the same structural model which was a two-compartment PK model with parallel linear and Michaelis-Menten elimination with first-order absorption for SC administration. The model for TCZ PK in RA was the starting point for the GCA population.

In both populations, the QW regimen resulted in nearly complete target saturation at steady-state during the entire dosing interval. The contribution of nonlinear CL to total CL was small at this dose.

In both populations, the target-mediated elimination pathway was not saturated during the entire dosing interval for the Q2W regimen which led to high total CL and high fluctuation of CL over dosing interval. The nonlinear CL led to a more than dose-proportional increase in steady state concentration for the QW regimen compared to the Q2W regimen.

In both populations, the PK parameters of TCZ following SC administration were not time-dependent as TCZ exposure was stable after achieving steady state.

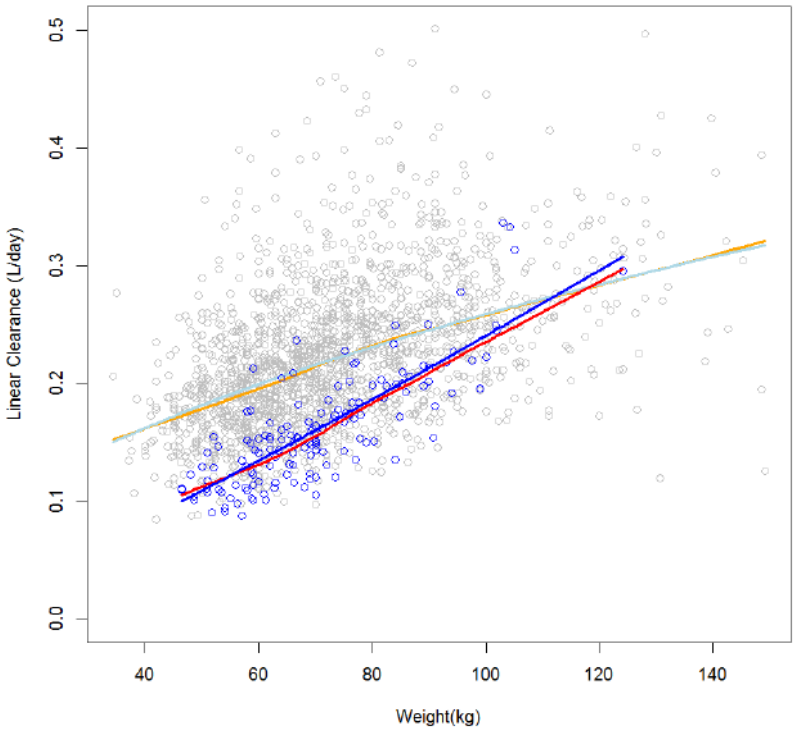
TCZ steady-state Ctrough values in GCA patients were 67.9±34.4 µg/mL and 12.2±10 µg/mL in the SC QW and Q2W group, respectively. Both mean steady state levels are slightly higher than observed in RA patients applying the same dose regimen (45 µg/mL and 5.9 µg/mL, respectively in RA patients).

Accumulation was much higher in the QW regimen which is plausible. CHMP agreed that the large increase in exposure between QW dosing and Q2W dosing is consistent with the known non-linear PK behaviour of TCZ.

BW influence on Ctrough exposure levels in GCA patients revealed a trend of higher Ctrough levels in lighter patients which is consistent with the use of a flat dose and with previous observations in RA patients. However, this impact was notably higher compared to RA patients. As the body weight ranges are comparative among both patient groups, body weight cannot be considered as reason for this notable difference in exposure between RA and GCA patients. The slightly higher levels observed in responder vs non-responder is not large enough to explain possible differences between GCA and RA.

Estimate of linear CL in GCA patients was slightly lower (approximately 30%) than in the RA population resulting in a higher exposure. This led to differences in the estimated half-life of TCZ and time to steady state in the two populations For example, the effective half-life at steady-state ranged from 12.1 to 13.0 days for the QW regimen in RA relative to 17.6 to 18.5 days for the same dose in GCA. After multiple dosing with the QW regimen, steady-state for AUC and Ctrough was achieved after the 12th injection in the RA population relative to the 16th injection in GCA.

In conclusion, a difference between the two populations was seen both on linear apparent CL and on the effect of body weight on linear apparent CL (see figure below). GCA patients appear to have a lower linear apparent CL than RA; the reason for the difference is unknown.



Note: Individual estimates of CL for patients with RA and patients with GCA are plotted versus individual body weight. Parameters (CL) were estimated using the SC RA model and the final model of the current analysis (GCA patients). Lowess smoothing lines and lines illustrating the clearance versus weight dependencies estimated by the models are shown for the comparison.
Gray circles: CL values for patients with RA; light blue line: dependence of CL on weight estimated by the final model for patients with RA; orange line: lowess smoothing line of the dependence of CL on weight for patients with RA.
Blue circles: CL values for patients with GCA; blue line: dependence of CL on weight estimated by the final model for patients with GCA; red line: lowess smoothing line of the dependence of CL on weight for patients with GCA.

The resultant impact of differences in linear apparent CL and KM in the two models results in a 50% difference between the predicted steady state exposures in the two populations. These differences are clearly stated in the SmPC Section 5.2 accordingly. These differences occur due to unknown reasons. PK differences are not accompanied by marked differences in PD parameters and so the clinical relevance is unknown.

Age might be a potential factor considering that in the study WA28119 in patients were about 15 years older than the previous RA studies, in this study the mean (range) age was 69.4 years (51 to 91 years). But none of the POP-PK models applied so far identified age as a significant variable.

GCA Patients

Treatment Arm	N	AUCτ (µg/mL*day)	C_{mean} (µg/mL)	C_{max} (µg/mL)	T_{max} (day)	C_{trough} (µg/mL)
Mean (SD)						
TCZ SC 162 mg QW	100	499.2 (210.4)	71.3 (30.1)	73.0 (30.4)	3 (0.1)	68.1 (29.5)
TCZ SC 162 mg Q2W	49	227.2 (165.4)	16.2 (11.8)	19.3 (12.8)	4.7 (0.6)	11.1 (10.3)
Median [Range]						
TCZ SC 162 mg QW	100	494.5 [82-1041.5]	70.6 [11.7-148.8]	72.1 [12.2-151]	3 [2.5-3]	67.2 [10.7-144.5]
TCZ SC 162 mg Q2W	49	191.3 [7.7-685.9]	13.7 [0.5-49]	17.2 [1.1-56.2]	4.5 [2.5-6]	7.7 [0.1-37.3]

RA Patients

Dose Regimen	N	AUC_{τ} (µg/mL*day)	C_{mean} (µg/mL)	C_{max} (µg/mL)	T_{max} (day)	C_{trough} (µg/mL)
Mean (SD)						
TCZ SC 162 mg QW	621	343.9 (159.7)	49.1 (22.8)	51.3 (23.2)	2.8 (0.2)	45.3 (22.2)
TCZ SC 162 mg Q2W	509	144.2 (105.5)	10.3 (7.5)	13.0 (8.3)	4.7 (0.5)	5.9 (6.3)
Median [range]						
TCZ SC 162 mg QW	621	332.5 [16.3-1038]	47.5 [2.3-148.3]	49.6 [2.9-150.1]	2.8 [1.9-3.6]	43.1 [1.3-145.2]
TCZ SC 162 mg Q2W	509	120 [3-607.5]	8.6 [0.2-43.4]	11.1 [0.4-48.7]	4.8 [1.6-6.4]	4.1 [0-34.4]

GCA = Giant cell arteritis; N = number of patients; QW = once a week; Q2W = once in every 2 weeks; RA = Rheumatoid arthritis; SC = subcutaneous; SD = standard deviation

Note: Concentrations of reference patient with RA and with GCA following TCZ QW and Q2W regimens were simulated using the RA SC model and the final model GCA model. Inter-subject and residual variability were not included. No covariate effects were included.

Despite the difference in PK, the post-dose sIL-6R levels were similar in the two populations indicating similarity in the contribution of the target mediated clearance in the two populations.

The sIL-6R responses to both QW and Q2W TCZ regimens are comparable to the mean levels in the same regimens in RA patients. In the RA study WA22762, sIL-6R levels in the QW regimen at steady state (Week 24) were 648 ± 189.3 ng/mL [n = 557] compared to 600.53 ± 217.52 ng/mL in the GCA study, WA28119. Similarly for the Q2W regimen sIL-6R levels were 449 ± 217.8 ng/mL [n = 346] in the RA study NA25220 relative to 464.30 ± 153.64 ng/mL in the GCA study, WA28119. Thus, post-dose sIL-6R levels were similar indicating similarity in the contribution of the target mediated CL in the two populations. Time courses of the PD biomarkers sIL-6R and IL-6 are in line with the expectations.

ADA incidence was low in both groups (1-6 %) which is comparable to the incidence previously observed in other populations. Given the low number of patients with positive treatment emerging ADA and the mixed influence on PK, CHMP concluded that there is no consistent impact of positive post-baseline anti-TCZ antibodies on PK, safety or efficacy of TCZ.

Population PK analysis

The data set comprised 1263 serum TCZ concentrations from a total of 149 GCA patients treated with TCZ over 52 weeks. Patients were treated with placebo or TCZ 162 mg, QW or Q2W SC for 52 weeks.

A 2-compartmental model that was previously established for RA patients (Model 317) was selected as basis to describe the PK of TCZ following multiple SC administration in GCA patients.

Typical PK parameters have been estimated (Model 107) and are in the range of typical values for a monoclonal antibody (CL: 0.16 L/day, Vc: 4.09 L, Vp: 3.37 L).

The significant covariates identified for GCA patients were: body weight on linear CL, Q, Vc, and Vp; age on Ka, and injection in the thigh on Fsc. The data set included relatively narrow range of ages (51 to 91 years), which leads to a high relative standard error estimated for the age effect on Ka. Therefore, age effect on Ka was fixed to be equal to the value in the adult RA model.

The parameter estimates were also in a good agreement with the prior model except for the parameter KM that was estimated to be higher for GCA patients (0.705 µg/mL in the current analysis versus 0.343 µg/mL estimated for adult RA patients). As indicated above, GCA patients appear to have a lower linear apparent clearance compared to RA patients.

Post hoc simulation of Ctrough exposure showed comparable mean concentration time profiles over 52 weeks compared to the observed values, which was also demonstrated by prognostic and VPC plots.

Body weight is the main covariate which has an appreciable impact on the PK of TCZ (Cl, V).

This impact was notably higher compared to RA patients. CL and Vc for patients weighting 48.6 kg (2.5th percentile of the weight distribution in the dataset) decreased respectively by 34% and 22% compared to a 70 kg patient. CL and Vc for patients weighting 102 kg (97.5th percentile of the weight distribution in the dataset) increased respectively by 54% and 29% compared to a 70 kg patient.

As the body weight ranges are comparative among both patient groups, body weight cannot be considered as reason for this notable difference in exposure between RA and GCA patients. The slightly higher levels observed in responder vs non-responder is not large enough to explain possible differences between GCA and RA.

Exposure-response analysis

Results showed that patients in the QW group achieved a range of exposures which provided the maximal possible benefit.

Tertile analysis showed that primary efficacy endpoints (sustained remission up to Week 52) were similar in all TCZ exposure categories with a small, but not statistically significant trend of increasing efficacy with exposure.

Patients in the 1st tertile in the Q2W group were at a higher risk for an earlier time to flare. Gender was also identified as a statistically significant predictor for the risk of flare with females identified as being at a higher risk. Risk of flare for males was ~3 times lower compared to females (HR = 0.320). The generalizability and the clinical significance of this gender effect are unknown and were further explored. Response rate difference between the placebo (PBO 26 wk) and treatment groups (TCZ Q2W) are essentially the same (the difference is 38.8% for female and 31.3% for male patients).

The reference for the effect of TCZ exposure is Cave8=3.346 µg/mL (=EC50 value). This finding may be influenced by the fact that 75% of the study participants were female due to a higher prevalence of GCA in females. No other prognostic factors had a significant effect on the risk of flare in GCA patients.

Data analysis showed the trend that about one third (lowest exposure tertile) of the patients in the Q2W

treatment group would gain benefit due to a higher exposure (Ctrough at week 52). Given that the weekly regimen is envisaged, this is considered acceptable by CHMP.

No clear exposure-safety relationship could be detected. There was a trend of greater decline of haematology parameters (white blood cells, neutrophils, and platelets) with increasing exposure, which reached a plateau at higher exposure levels for white blood cell and neutrophil counts. There was no association of TCZ concentrations with the occurrence of neutropenia or thrombocytopenia.

Given that there is a higher exposure in GCA patients compared to RA patients and comparatively low patient numbers, exposure-safety relationships were discussed including the neutrophil loss rate. Higher exposure in the GCA population did not lead to clinically relevant differences in safety outcomes relative to the RA population.

Interactions

IL-6 is known to suppress the expression levels of the mRNAs that code for drug metabolizing enzymes (cytochrome P450 enzymes [CYPs]). This fact known from the literature had been confirmed by in-vitro studies, and the effect was particularly pronounced regarding to CYP3A4. TCZ was able to block this effect of Il-6 at therapeutic plasma concentrations. When the function of IL-6 is inhibited in such patients by the administration of TCZ, CYP expression levels may rise above pre-dosing levels and the serum concentrations of coadministered drugs that are metabolized by CYPs may decrease. This has been shown in RA patients using simvastatin as probe molecule. In a study in RA patients levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of tocilizumab. Oral glucocorticoids (OGC) (methylprednisolone, dexamethasone) are metabolized by this CYP3A4 so plasma OGC level can decrease much faster than planned. The increased elimination carries the risk of decreased efficacy of OGC when it is co-administered with TCZ in the OCG taper period. There is also the risk of glucocorticoid withdrawal syndrome. As the issue is not specific for GCA and also relevant of other approved indications such as RA and sJIA, methylprednisolone and dexamethasone have been added to the list of interacting drugs in Section 4.5 with an added warning of GC withdrawal syndrome.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data submitted is considered acceptable by CHMP to support the use of tocilizumab in patients with GCA.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose response studies were conducted.

The rationale for the TCZ doses to be investigated in Study WA28119 was based on the 31 case reports of GCA patients who had been dosed with the approved RA doses of TCZ (4 mg/kg and 8 mg/kg IV every 4 weeks [Q4W]) at the time of study start; 29 patients had received 8 mg/kg IV every 4 weeks (in some cases the starting dose was 8 mg/kg every 2 weeks), and 2 patients had received 4 mg/kg IV every 4 weeks (Seitz et al. 2011; Christidis et al. 2011; Beyer et al. 2011; Salvarani et al. 2012; Unizony et al. 2012; Roche data on file). Patients responded well, and no treatment-limiting safety concerns were noted. In the patients dosed with TCZ 8 mg/kg, PD data showed a decrease in post-dose CRP and an increase in post-dose IL-6 levels. The normalization of CRP was sustained throughout the 4-week dosing interval, suggesting adequate blockade of IL-6 signaling in GCA with TCZ 8 mg/kg IV Q4W.

For Study WA28119, the SC route of administration, via pre-filled syringe (PFS), was chosen over the IV route as it provides a more convenient route of administration in the elderly population of patients with GCA (e.g., home administration, no requirement for venous access). The two SC doses selected in the Phase III RA SC program (162 mg QW and Q2W) were assessed. The 162 mg SC QW dose had PD profiles comparable to those for the approved 8 mg/kg Q4W IV dose in RA patients (Study MRA227JP; Study NP22623) and was expected to also show a similar PK/PD profile in GCA patients. This dose was expected to deliver optimized efficacy and safety in GCA. The dose of 162 mg SC Q2W is a lower SC dose option that was expected to deliver an acceptable safety profile with reasonable efficacy.

The CHMP considered acceptable that no dose response studies were conducted since two TCZ doses were studied in phase III WAS28119 study.

2.4.2. Main study

A Phase III, multicentre, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in subjects with giant cell arteritis (WA28119)

Methods

Study participants

The target population for this study were adult patients with GCA who have active disease (signs and symptoms and elevated ESR) within the 6 weeks prior to baseline visit. New-onset and relapsed/refractory GCA patients are eligible. New-onset and relapsing disease were defined as follows:

- New-onset: diagnosis of active GCA within 6 weeks of baseline visit (defined as the presence of clinical signs and symptoms and ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL; elevations in ESR and CRP were not required if the patient had a positive temporal artery biopsy within the 6 weeks prior to baseline).
- Relapsing: diagnosis of GCA > 6 weeks before baseline visit, previous treatment with ≥ 40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at any time, and active GCA within 6 weeks of baseline visit (defined as the presence of clinical signs and symptoms and ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL; elevations in ESR and CRP were not required if the patient had a positive temporal artery biopsy within the 6 weeks prior to baseline). This included patients who had previously achieved remission and subsequently flared and those who had not achieved remission since the diagnosis of disease (i.e., refractory patients).

A screening period of 6 weeks was defined for the purpose of distinguishing between new-onset and relapsing patients.

Key inclusion criteria

Diagnosis of GCA classified according to the following criteria:

- Age ≥ 50 years
- History of ESR ≥ 50 mm/hour*

* If historic ESR was unavailable, a history of CRP ≥ 2.45 mg/dL was required. The CRP value was derived from published data both from GCA and RA patients (Hayreh et al. 1997; Wolfe 1997; Paulus et al. 1999).

AND at least one of the following:

- Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)
- Symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

AND at least one of the following:

- Temporal artery biopsy revealing features of GCA
- Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRA, CTA, or PET-CT

New-onset or relapsing active disease defined as follows:

- New-onset: diagnosis* of GCA within 6 weeks of baseline visit
- Relapsing: diagnosis of GCA > 6 weeks before baseline visit and previous treatment with ≥ 40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at any time

* The 6 week time window had to be calculated from the date of suspected GCA diagnosis. Suspected diagnosis was defined as the date when glucocorticoid therapy was initiated to treat suspected GCA.

AND

- Active GCA within 6 weeks of baseline visit (active disease defined as the presence of clinical signs and symptoms [cranial or PMR] and ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL).
  ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL was not required if active GCA had been confirmed by a positive temporal artery biopsy within 6 weeks of the baseline visit

Key exclusion criteria

General exclusion criteria

Major surgery within 8 weeks prior to screening or planned major surgery within 12 months after randomization

Transplanted organs (except corneal transplant performed more than 3 months prior to screening)

Major ischemic event, unrelated to GCA, within 12 weeks of screening

The main exclusion criteria related to:

Patients requiring systemic glucocorticoids for conditions other than GCA, which, in the opinion of the investigator, would interfere with adherence to the fixed glucocorticoid taper regimen and/or to assessment of efficacy in response to the test article

Chronic use of systemic glucocorticoids for > 4 years or inability, in the opinion of the investigator, to withdraw glucocorticoid treatment through protocol-defined taper regimen due to suspected or established adrenal insufficiency

Receipt of > 100 mg daily intravenous methylprednisolone within 6 weeks of Baseline

Active tuberculosis requiring treatment within the previous 3 years

Treatments

Patients were randomized in a 1:1:2:1 ratio into four groups:

- Placebo SC weekly (QW) + 26-week prednisone taper regimen (PBO + 26 wk; n = 50)
- Placebo SC QW + 52-week prednisone taper regimen (PBO + 52 wk; n = 51)
- 162 mg TCZ SC QW + 26-week prednisone taper regimen (TCZ QW; n = 100)
- 162 mg TCZ SC every other week (Q2W) + 26-week prednisone taper regimen (TCZ Q2W; n = 50)

During the screening period, patients could receive glucocorticoids for the treatment of GCA at the discretion of the investigator. By the end of the screening period, patients had to switch to the Sponsor-provided prednisone in order to follow the protocol-defined prednisone taper. At the time of the baseline visit, all patients had to switch from the glucocorticoid prescribed by the investigator to prednisone provided by the Sponsor. The baseline daily dose had to be within the range of prednisone 20—60 mg/day.

Calcium, bisphosphonates, vitamin D, anti-platelet therapy, lipid-lowering agents, and MTX are allowed as concomitant medication.

Objectives

Primary efficacy objective: To evaluate the efficacy of TCZ compared to placebo, in combination with a 26-week prednisone taper regimen, in patients with GCA, as measured by the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined prednisone taper regimen.

- Induction of remission had to occur within 12 weeks of randomization.
- Sustained remission was defined as absence of flare following induction of remission up to the 52-week time point.
    - Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or erythrocyte sedimentation rate (ESR) ≥ 30 mm/h attributable to GCA.
- Patients had to follow the protocol-defined prednisone taper regimen

Remission was defined as the absence of flare (as defined above) and normalisation of C-reactive protein (CRP < 1 mg/dL).

Key secondary objectives of the study: To evaluate the efficacy of TCZ in combination with a 26-week prednisone taper regimen versus placebo in combination with the 52-week prednisone taper regimen, in patients with GCA, as measured by the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined prednisone taper regimen.

Other secondary objectives:

- To assess the efficacy of TCZ in combination with a 26-week prednisone taper regimen versus both placebo groups in patients with GCA, as measured by the following:
    - Time to GCA disease flare after clinical remission
    - Cumulative glucocorticoid dose
- To assess the effect on patient's quality of life of TCZ in combination with a 26-week prednisone taper regimen versus both placebo groups in patients with GCA, based on the patient-reported

outcome (PRO) as measured by SF-36 and patient global assessment (PGA) of disease activity on a visual analogue scale (VAS).

To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in combination with a 26-week prednisone taper regimen in patients with GCA.

Outcomes / endpoints

The primary efficacy endpoint is the proportion of patients in sustained remission at Week 52.

The key secondary efficacy endpoint was the proportion of patients in sustained remission at Week 52 in the TCZ groups in combination with a 26-week prednisone taper regimen compared with the placebo + 52-week prednisone taper.

The secondary efficacy endpoints are as follows:

- Time to first GCA disease flare after clinical remission (up to 52 weeks)
- Summary of total cumulative prednisone dose over 52 weeks
- Change from baseline in SF-36 (Physical and Mental Component Summaries) at 52 weeks
- Change from baseline in PGA of disease activity (VAS scale) at 52 weeks

Sample size

Assuming that the absolute difference in the proportion of patients who are in sustained remission at 52 weeks is equal to 40% (assuming ρTCZ = 70% versus ρ6-mCS = 30%), a sample size of 100 patients in the 162qw TCZ group and 50 patients in both the 162 q2w TCZ group and placebo group (in combination with the 26-week prednisone taper group) will ensure at least 90% power to detect a difference in the proportion of patients in sustained remission at Week 52 for both TCZ arms versus placebo at an alpha level of 0.01 (2-sided). In addition, 50 patients will also be included in the 52-week prednisone taper group.

Randomisation

Patients were randomly assigned in a 1:1:2:1 ratio to treatment arms and randomization was stratified by the baseline prednisone dose (> 30 mg/day, ≤ 30 mg/day prednisone).

The proportion of relapsing patients (GCA diagnosed > 6 weeks before the baseline visit and previous treatment with ≥ 40 mg/day prednisone or equivalent for ≥ 2 consecutive weeks at any time) enrolled was preferentially limited to 70% to ensure some enrolment of new-onset patients (GCA diagnosed within 6 weeks of the baseline visit) but could be increased depending on the rate of enrolment of relapsing versus new-onset patients.

Blinding (masking)

The study was double-blinded during the first 52 weeks and to maintain the blinding of treatment allocation a Dual Assessor Approach was utilized. As knowledge of certain laboratory data could result in inadvertent unblinding of a patient's treatment, in order to maintain the blind, a Laboratory Assessor was assigned who was responsible for the overall clinical management of the patient outside of their GCA. ESR was measured at each visit and all site personnel, including the Clinical Assessor, were blinded to the results with the exception of the Laboratory Assessor and the Study Coordinator/ESR technician.

Unblinding by the Sponsor occurred at the time of the Week 52 primary analysis. Per regulatory requirements, study treatment was to be unblinded for all unexpected serious adverse events (SAEs) that were considered by the investigator to be related to study drug.

Statistical methods

There were 5 pre-defined analysis sets: the all-patients set (all randomized patients), the ITT set (randomized patients with at least one dose of TCZ/placebo), the PK-evaluable set, the safety set and the escape population (ITT patients who entered escape therapy). The primary analysis population for all efficacy analyses was the intent-to-treat (ITT) population.

The primary endpoint, proportion of patients in sustained remission at Week 52, was analysed using a Cochran-Mantel-Haenszel (CMH) test for the ITT population, adjusting for starting prednisone dose (≤ 30 mg/day, > 30 mg/day), which was the stratification factor applied at randomization. Non-responder imputation was used for missing data. A tipping point analysis was performed to assess the robustness of the primary analysis. A second sensitivity analysis was performed for disease diagnosis based on signs and symptoms of disease only in order to mitigate against the possibility of biasing the results because of the known PD effect of TCZ on acute phase reactants.

The key secondary efficacy endpoint was the proportion of patients in sustained remission at Week 52 in the TCZ groups in combination with a 26-week prednisone taper regimen compared with the placebo + 52- week prednisone taper group. In order to determine non-inferiority, a two-sided 99.5% CI was constructed for the difference in proportions between each TCZ group and the placebo + 52-week taper group on the basis of the normal approximation and adjusted for the prednisone starting dose and compared to a non-inferiority margin of -22.5% which was defined in the SAP but not in the study protocol. The non-inferiority margin was derived based on one study (Seror et al. 2014) with a prednisone response rate of 71% (95% CI: 52%-86%) and a placebo response rate of 0% (95% CI: 0%-7%). Further 8 studies were listed but not used for the derivation of the non-inferiority margin as they used a different taper regimen or were retrospective, observational studies. Post-hoc analyses of the difference in proportions was performed using an extended Mantel-Haenszel test based on the normal approximation and was adjusted for the baseline stratification factor of prednisone starting dose (≤ 30 mg/day, > 30 mg/day).

The primary and key secondary endpoints were tested at a 1% overall significance level ($\alpha = 0.01$) against two-sided alternatives. The SAP specified two independent hierarchies for the TCZ dose families for which the overall alpha level was equally divided (i.e., $\alpha = 0.5\%$ per family) in order to correct the type I error rate for multiple comparisons. Both hierarchies tested the treatment comparisons in a fixed sequential order as specified in the SAP to further control for multiplicity.

Hierarchy 1 tested the primary endpoint for superiority of TCZ QW + 26-week prednisone taper versus placebo + 26-week prednisone taper, followed by the key secondary endpoint for non-inferiority of TCZ QW + 26-week prednisone taper versus placebo + 52-week prednisone taper.

Hierarchy 2 tested the primary endpoint for superiority of TCZ Q2W + 26-week prednisone taper versus placebo + 26-week prednisone taper, followed by the key secondary endpoint for non-inferiority of TCZ Q2W + 26-week prednisone taper versus placebo + 52-week prednisone taper.

All other secondary and exploratory endpoints were not controlled for multiplicity.

However, the key secondary endpoint was also tested for superiority after non-inferiority was met using a Cochran Mantel-Haenszel test based on the normal approximation adjusted for the baseline stratification factor of prednisone starting dose (≤ 30 mg/day, > 30 mg/day).

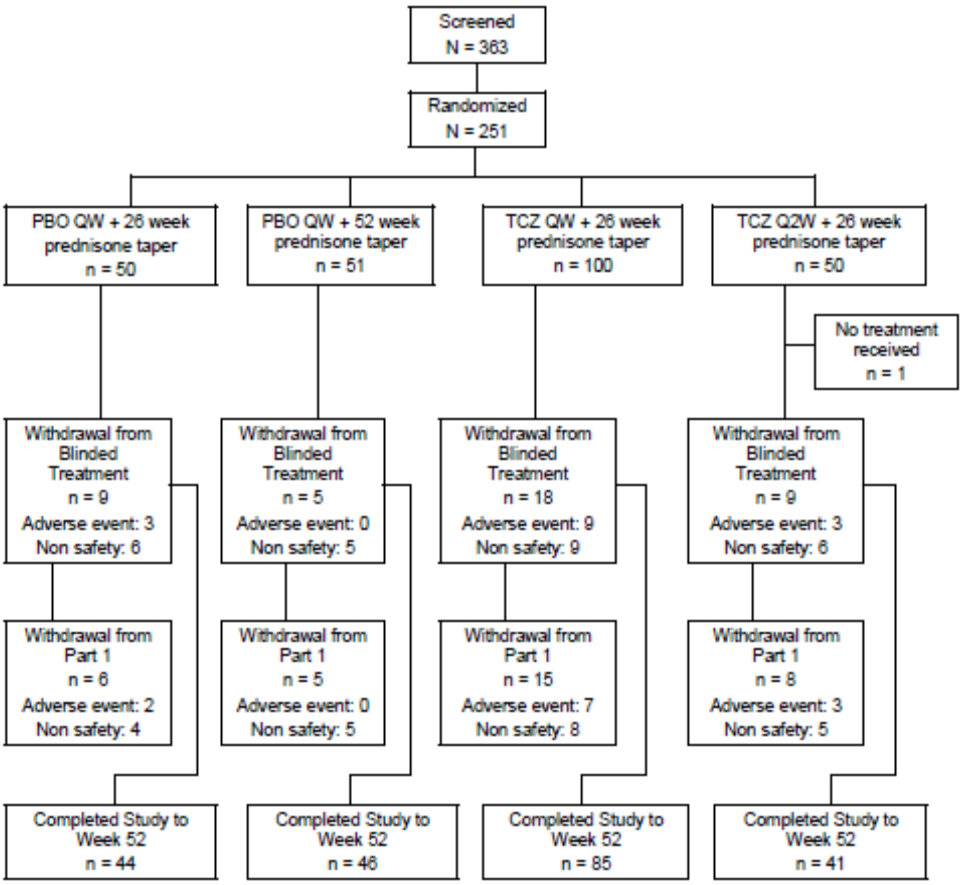
Each of the TCZ treatment groups was compared with both placebo groups for further secondary endpoints. Time to disease flare was analysed using time-to-event methods based on the Kaplan-Meier estimator and Cox PH model with stratification factor starting prednisone dose. The cumulative prednisone dose to Week 52 (including all taper prednisone [both open-label and blinded taper], escape therapy and commercial prednisone) was analysed using a van Elteren test stratified by starting prednisone dose on the basis of the assumption that total cumulative prednisone dose was non-normally distributed or on an appropriate parametric analysis stratifying by starting prednisone dose in case of normal distribution.

Change from baseline in PGA and SF-36 were analysed using a maximum likelihood-based repeated measures model with categorical effects for treatment, baseline prednisone dose (≤ 30 mg/day, > 30 mg/day), visit, treatment-by-visit interaction, and baseline prednisone dose-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. An unstructured variance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. A contrast between treatments at the Week 52 timepoint was the comparison of interest.

Results

Participant flow

Figure 10 - Overview of patient disposition



During the 52-week double-blind period (Part 1), a total of 41 patients were withdrawn prematurely from blinded study treatment (TCZ/placebo/prednisone): 9 patients (18%) in the PBO + 26 wk group, 5 patients

(10%) in the PBO + 52 wk group, 18 patients (18%) in the TCZ QW group and 9 patients (18%) in the TCZ Q2W group. The most common reason for premature discontinuation from study treatment was withdrawal because of an AE (see also below). Nine patients in the TCZ QW group, 7 patients in the TCZ Q2W group, 6 patients in the PBO + 26 wk group and 5 patients in the PBO + 52 wk group were withdrawn from study treatment due to non-safety reasons.

Table 4 - Reasons for patient withdrawal from blinded study treatment (All Patients)

Patients Discontinued from SC Double-Blind Study Treatment, All Patients Population
Protocol: WA28119

Status	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Patients who Completed DB Treatment	41 (82.0%)	46 (90.2%)	82 (82.0%)	40 (80.0%)
Discontinued by Week 52	9 (18.0%)	5 (9.8%)	18 (18.0%)	10 (20.0%)
Safety	3 (6.0%)	0	9 (9.0%)	3 (6.0%)
Adverse Event	3 (6.0%)	0	9 (9.0%)	3 (6.0%)
Pregnancy	0	0	0	0
Death	0	0	0	0
Non-Safety	6 (12.0%)	5 (9.8%)	9 (9.0%)	7 (14.0%)
Lost to follow-up	0	0	0	0
Non-compliance	0	0	1 (1.0%)	0
Lack of efficacy	1 (2.0%)	2 (3.9%)	1 (1.0%)	3 (6.0%)
Withdrawal by subject	2 (4.0%)	1 (2.0%)	5 (5.0%)	2 (4.0%)
Physician decision	3 (6.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
Protocol Violation	0	1 (2.0%)	0	0
Other	0	0	1 (1.0%)	1 (2.0%)
Reason Not Collected	0	0	0	0

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ds_disc.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ds_disc_AP.out 12JUL2016 13:14 (PDRD) Page 1 of 1

Recruitment

First patient screened: 15 July 2013

First patient randomized: 22 July 2013

Clinical cut-off for the analysis: 11 April 2016

Conduct of the study

The original protocol (dated 20 July 2012) was amended three times: on 19 October 2012 (Version 2), on 08 February 2013 (Version 3), on 07 June 2013 in Canada only (Version 4 Canada), and on 22 January 2014 (Version 4 globally, and Version 5 in Canada).

Version 2: dated, 19 October 2012. The most significant changes are related to:

- The inclusion criteria relating to the requirement for a history of ESR ≥ 50 mm/hour and active disease according to an ESR ≥ 30 mm/hour were clarified. The exclusion criteria were revised to exclude only major ischemic events unrelated to GCA and a new exclusion criterion added to exclude patients who received pulsed methylprednisolone within 6 weeks of baseline
- The protocol was aligned with the Sponsor's memorandum on "Implementing IgE Assay for TCZ Immunogenicity Testing" and immunogenicity testing for patients who discontinued treatment with TCZ was added

Version 3: dated, 08 February 2013. The most significant changes are related to:

- Following FDA feedback the definition of relapsing patients was updated to include those with active disease despite at least 2 consecutive weeks of treatment with ≥ 40 mg/day prednisone (or equivalent) at any time.
- Following FDA feedback the key secondary endpoint defining a comparison of the proportion of patients in sustained remission at Week 52 in the TCZ groups versus the placebo group with 52-week prednisone taper was added.

Version 4: dated, 22 January 2014. The most significant changes are related to:

- To better reflect clinical practice where CRP is replacing ESR in several health centres, the requirement for a CRP ≥ 2.45 mg/dL for patients where a historical ESR value was unavailable was added.
- Removal of the requirement of ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL to confirm active disease in patients with a positive temporal artery biopsy within 6 weeks of baseline.
- Definition of flare was modified to allow the clinical assessor to consider an elevated ESR as disease flare in the absence of GCA signs and symptoms if, in their opinion, it was attributable to GCA.

Protocol deviations

Table 5 - Violations of protocol eligibility criteria

Patient	Treatment Group	Eligibility Violation
		Inclusion Criterion No. 2
255505/11103	TCZ QW	Available historical ESR value was below 50 mm/hr.
255207/10046	PBO + 26 wk	Available historical ESR value was below 50 mm/hr.
255211/10402	TCZ Q2W	Patient had no documented historical ESR values.
		Inclusion Criterion No. 3
255201/10001	PBO + 26 wk	Patient was randomized outside 6 week window since last ESR assessment.
255724/10081	TCZ QW	Patient was randomized outside 6 week window since last ESR assessment.
265086/10922	TCZ Q2W	Patient did not have a documented ESR≥30 mm/hr or a CRP≥1 mg/dL within 6 weeks of the baseline visit.
		Exclusion Criterion No. 16
255771/10362	TCZ Q2W	Patients received>100 mg daily IV methylprednisolone within 6 weeks of baseline.
253740/10242	PBO + 26 wk	
255251/10228	TCZ QW	
		Exclusion Criterion No. 22
255730/11341	TCZ Q2W	Patient was randomized despite the fact that the patient was suffering from a urinary tract infection requiring antibiotics.
		Exclusion Criterion No. 23
255251/10222	PBO + 52 wk	Patients were not screened for active TB within 42 days of the baseline visit or for latent TB within 3 weeks of baseline.
255724/10321	TCZ Q2W	
253746/10143	TCZ QW	
255730/11341	TCZ Q2W	
		Exclusion Criterion No. 37
255226/10864	PBO + 26 wk	Absolute lymphocyte count<0.5 x 10^9/L (500/mm^3)

Five patients deviated from the protocol-defined prednisone taper. Patients who deviated from the protocol defined prednisone taper were placed back onto the prednisone dose they should have been receiving. If the patient was ahead of the predefined taper schedule then an extra wallet was inserted into the taper schedule via the IVRS and if the patient was behind the predefined taper schedule they were placed onto the correct prednisone taper wallet.

Baseline data

Table 6 - Summary of demographic data at baseline (all patients)

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Age (years)				
n	50	51	100	50
Mean (SD)	69.3 (8.1)	67.8 (7.7)	69.5 (8.5)	69.4 (8.2)
Median	70.5	68.0	71.0	71.0
Min - Max	52 - 83	52 - 84	51 - 85	53 - 91
Age group (years)				
n	50	51	100	50
< 65 years	16 (32.0%)	17 (33.3%)	32 (32.0%)	17 (34.0%)
>= 65 years	34 (68.0%)	34 (66.7%)	68 (68.0%)	33 (66.0%)
Sex				
n	50	51	100	50
Male	12 (24.0%)	14 (27.5%)	22 (22.0%)	15 (30.0%)
Female	38 (76.0%)	37 (72.5%)	78 (78.0%)	35 (70.0%)
Ethnicity				
n	50	51	100	50
Hispanic or Latino	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
Not Hispanic or Latino	49 (98.0%)	49 (96.1%)	96 (96.0%)	46 (92.0%)
Not Reported	0	1 (2.0%)	2 (2.0%)	2 (4.0%)
Unknown	1 (2.0%)	0	0	1 (2.0%)
Race				
n	50	51	100	50
Asian	0	0	0	1 (2.0%)
Black or African American	0	2 (3.9%)	1 (1.0%)	0
Other	0	0	1 (1.0%)	1 (2.0%)
White	50 (100.0%)	49 (96.1%)	97 (97.0%)	47 (94.0%)
Unknown	0	0	1 (1.0%)	1 (2.0%)
Weight (kg)				
n	50	51	100	49
Mean (SD)	70.12 (15.83)	73.13 (15.34)	69.82 (13.82)	70.84 (16.09)
Median	66.65	70.60	67.50	69.20
Min - Max	47.7 - 120.0	48.5 - 108.0	48.0 - 105.0	46.4 - 124.1
Height (cm)				
n	50	51	100	49
Mean (SD)	164.70 (9.51)	167.86 (8.45)	163.90 (10.08)	165.33 (9.09)
Median	162.80	167.00	163.00	167.70
Min - Max	139.7 - 188.0	153.0 - 191.0	125.3 - 187.0	139.0 - 184.0
BMI (kg/m2)				
n	50	51	100	49
Mean (SD)	25.70 (4.46)	25.80 (4.13)	25.97 (4.42)	25.99 (6.15)
Median	24.92	25.35	25.62	24.80
Min - Max	18.0 - 40.1	18.3 - 36.0	18.1 - 38.6	17.8 - 53.4
Smoking History				
n	50	51	100	49
Never	35 (70.0%)	29 (56.9%)	57 (57.0%)	28 (57.1%)
Current	7 (14.0%)	9 (17.6%)	13 (13.0%)	5 (10.2%)
Previous	8 (16.0%)	13 (25.5%)	30 (30.0%)	16 (32.7%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_dm.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_dm_AP.out
11JUL2016 21:21 (PDRD) Page 1 of 1

Table 7 - Summary of GCA disease characteristics at baseline (all patients)

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Duration of GCA (days)				
n	50	51	100	50
Mean (SD)	364.66 (569.85)	255.22 (435.45)	306.80 (563.50)	258.38 (500.68)
Median	80.00	53.00	52.00	41.50
Min - Max	12.0 - 2698.0	8.0 - 1789.0	9.0 - 2856.0	13.0 - 2708.0
Disease Onset				
n	50	51	100	50
New Patient	23 (46.0%)	23 (45.1%)	47 (47.0%)	26 (52.0%)
Relapse Patient	27 (54.0%)	28 (54.9%)	53 (53.0%)	24 (48.0%)
Prednisone dose at baseline (mg/day)				
n	50	51	100	49
Mean (SD)	34.60 (12.97)	34.48 (14.20)	34.60 (13.37)	35.92 (13.76)
Median	30.00	30.00	30.00	35.00
Min - Max	20.0 - 60.0	5.0 - 60.0	10.0 - 60.0	5.0 - 60.0
Prednisone dose (<=30mg/day, >30mg/day)				
n	50	51	100	50
=<30 mg/day	27 (54.0%)	26 (51.0%)	52 (52.0%)	25 (50.0%)
>30 mg/day	23 (46.0%)	25 (49.0%)	48 (48.0%)	25 (50.0%)
First steroid for GCA (mg)				
n	50	50	100	49
Mean (SD)	104.74 (197.94)	61.76 (44.95)	79.02 (143.91)	78.40 (150.75)
Median	60.00	60.00	60.00	50.00
Min - Max	20.0 - 1000.0	10.0 - 250.0	2.0 - 1000.0	5.0 - 1000.0
Baseline C-reactive protein (CRP) (mg/L)				
n	50	51	100	49
Mean (SD)	7.69 (10.32)	8.17 (21.00)	6.78 (8.70)	11.36 (25.38)
Median	3.64	3.56	3.67	4.52
Min - Max	0.2 - 47.1	0.2 - 149.0	0.2 - 45.5	0.2 - 154.0
Baseline erythrocyte sedimentation rate (ESR) (mm/h)				
n	50	51	99	49
Mean (SD)	28.77 (25.43)	24.22 (18.19)	24.62 (18.66)	20.78 (18.13)
Median	23.00	20.00	19.00	15.00
Min - Max	1.0 - 115.0	2.0 - 75.0	2.0 - 95.0	0.0 - 79.0
Patient's Global Assessment VAS (mm)				
n	49	51	100	49
Mean (SD)	35.73 (28.15)	47.78 (27.80)	43.61 (25.66)	46.65 (25.60)
Median	30.00	50.00	48.00	48.00
Min - Max	0.0 - 91.0	0.0 - 100.0	0.0 - 100.0	1.0 - 91.0
Overall EQ-5D Score				
n	50	49	99	49
Mean (SD)	0.742 (0.219)	0.662 (0.264)	0.736 (0.207)	0.737 (0.218)
Median	0.725	0.725	0.760	0.727
Min - Max	0.02 - 1.00	-0.18 - 1.00	-0.14 - 1.00	0.26 - 1.00
Overall FACIT Score				
n	50	49	99	49
Mean (SD)	35.04 (12.77)	31.42 (13.60)	36.05 (11.06)	36.27 (11.55)
Median	37.00	33.00	38.00	39.00
Min - Max	4.0 - 52.0	4.0 - 52.0	8.0 - 52.0	7.0 - 52.0

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
SF-36 Mental Component Score				
n	48	49	97	49
Mean (SD)	42.729 (12.132)	40.454 (13.726)	42.769 (12.427)	47.673 (12.593)
Median	42.715	37.863	44.142	48.018
Min - Max	16.08 - 62.20	8.72 - 62.50	8.17 - 68.23	18.04 - 67.51
SF-36 Physical Component Score				
n	48	49	97	49
Mean (SD)	42.647 (10.868)	41.117 (9.972)	43.097 (9.426)	40.618 (7.996)
Median	43.911	41.313	44.265	40.203
Min - Max	16.15 - 59.54	21.71 - 58.77	19.24 - 59.45	21.50 - 56.51
Signs and Symptoms				
n	50	51	100	50
Both	20 (40.0%)	24 (47.1%)	37 (37.0%)	23 (46.0%)
Cranial Only	20 (40.0%)	16 (31.4%)	41 (41.0%)	18 (36.0%)
PMR Only	10 (20.0%)	11 (21.6%)	22 (22.0%)	9 (18.0%)
Baseline Fever (38C or 100.4F)				
n	50	51	100	50
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	50 (100.0%)
Baseline Bilateral Blindness				
n	50	51	100	50
Yes	0	0	0	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (98.0%)
Baseline Ischemic Optic Neuropathy				
n	50	51	100	50
Yes	0	0	1 (1.0%)	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	99 (99.0%)	49 (98.0%)
Baseline Amaurosis Fugax				
n	50	51	100	50
Yes	0	0	1 (1.0%)	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	99 (99.0%)	49 (98.0%)
Baseline Blurred Vision				
n	50	51	100	50
Yes	2 (4.0%)	5 (9.8%)	4 (4.0%)	3 (6.0%)
No	48 (96.0%)	46 (90.2%)	96 (96.0%)	47 (94.0%)
Baseline Diplopia				
n	50	51	100	50
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	50 (100.0%)
Baseline Unilateral Blindness				
n	50	51	100	50
Yes	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
No	49 (98.0%)	50 (98.0%)	99 (99.0%)	49 (98.0%)

GCA disease characteristics

Table 8 - Summary of GCA disease features at diagnosis (all patients)

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Age > 50 years				
n	50	51	100	50
Yes	50 (100.0%)	51 (100.0%)	100 (100.0%)	50 (100.0%)
History of ESR > 50 mm/hour				
n	50	51	100	50
Yes	49 (98.0%)	51 (100.0%)	94 (94.0%)	47 (94.0%)
No	1 (2.0%)	0	6 (6.0%)	3 (6.0%)
History of CRP > 2.45 mg/d				
n	50	51	100	50
Yes	41 (82.0%)	38 (74.5%)	87 (87.0%)	43 (86.0%)
No	9 (18.0%)	13 (25.5%)	13 (13.0%)	7 (14.0%)
New onset localized headache				
n	50	51	100	50
Yes	29 (58.0%)	34 (66.7%)	68 (68.0%)	38 (76.0%)
No	21 (42.0%)	17 (33.3%)	32 (32.0%)	12 (24.0%)
Scalp tenderness				
n	50	51	100	50
Yes	16 (32.0%)	16 (31.4%)	38 (38.0%)	20 (40.0%)
No	34 (68.0%)	35 (68.6%)	62 (62.0%)	30 (60.0%)
Temporal artery tenderness				
n	50	51	100	50
Yes	14 (28.0%)	14 (27.5%)	26 (26.0%)	18 (36.0%)
No	36 (72.0%)	37 (72.5%)	74 (74.0%)	32 (64.0%)
Temporal artery decreased pulsation				
n	50	51	100	50
Yes	8 (16.0%)	6 (11.8%)	7 (7.0%)	8 (16.0%)
No	42 (84.0%)	45 (88.2%)	93 (93.0%)	42 (84.0%)
Ischemia-related vision loss				
n	50	51	100	50
Yes	7 (14.0%)	4 (7.8%)	7 (7.0%)	7 (14.0%)
No	43 (86.0%)	47 (92.2%)	93 (93.0%)	43 (86.0%)
Otherwise unexplained mouth or jaw pain upon mastication				
n	50	51	100	50
Yes	20 (40.0%)	15 (29.4%)	31 (31.0%)	19 (38.0%)
No	30 (60.0%)	36 (70.6%)	69 (69.0%)	31 (62.0%)
Symptoms of PMR				
n	50	51	100	50
Yes	30 (60.0%)	35 (68.6%)	59 (59.0%)	32 (64.0%)
No	20 (40.0%)	16 (31.4%)	41 (41.0%)	18 (36.0%)
Was TAB performed?				
n	50	51	100	50
Yes	38 (76.0%)	33 (64.7%)	64 (64.0%)	37 (74.0%)
No	12 (24.0%)	18 (35.3%)	36 (36.0%)	13 (26.0%)
Positive TAB				
n	38	33	64	37
Yes	36 (94.7%)	29 (87.9%)	57 (89.1%)	34 (91.9%)
No	2 (5.3%)	4 (12.1%)	7 (10.9%)	3 (8.1%)

Program: /opt/BIOSTAT/prod/cm11935e/i28119a/t_diag.sas / Output:

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Positive imaging study?				
n	50	51	100	50
Yes	19 (38.0%)	23 (45.1%)	50 (50.0%)	23 (46.0%)
No	31 (62.0%)	28 (54.9%)	50 (50.0%)	27 (54.0%)
Active GCA within 6 Weeks of Baseline				
n	50	51	100	50
Yes	50 (100.0%)	50 (98.0%)	100 (100.0%)	50 (100.0%)
No	0	1 (2.0%)	0	0
Has patient ever been in remission				
n	50	51	100	50
Yes	20 (40.0%)	19 (37.3%)	46 (46.0%)	22 (44.0%)
No	30 (60.0%)	32 (62.7%)	54 (54.0%)	28 (56.0%)
Was an imaging study performed?				
n	27	27	58	27
CTA	1 (3.7%)	1 (3.7%)	7 (12.1%)	4 (14.8%)
MRA	1 (3.7%)	0	6 (10.3%)	1 (3.7%)
MRI	3 (11.1%)	1 (3.7%)	1 (1.7%)	1 (3.7%)
PET-CT	18 (66.7%)	21 (77.8%)	39 (67.2%)	19 (70.4%)
Other	4 (14.8%)	4 (14.8%)	5 (8.6%)	2 (7.4%)

Program: /opt/BIOSTAT/prod/cm11935e/i28119a/t_diag.sas / Output:
/opt/BIOSTAT/prod/cm11935e/i28119a/reports/t_diag_AP.out
11JUL2016 21:24 (PDRD)

Page 2 of 2

Prednisone dose at baseline

Median prednisone dose at baseline (start of the open-label prednisone taper period) was 35 mg/day (range 5-60 mg) in the TCZ Q2W group and 30 mg/day (range 5-60 mg) in all other treatment groups. Per protocol, patients were to be receiving a starting prednisone dose of 20-60 mg/day at baseline (i.e., 60/50/40/35/30/25 or 20 mg/day). However, 5 patients received the incorrect dose of prednisone at baseline in error. These prednisone starting dose errors were captured as major protocol deviations, although the patients were permitted to remain in the study (see above). Two further patients had prednisone dosing medication errors at baseline one in the PBO + 52 wk group and one patient in the TCZ QW group. These prednisone medication errors were not captured as protocol violations.

All but one of the patients with incorrect prednisone starting doses experienced remission post-baseline.

Analysis of prednisone starting dose by incremental categories (20, 25, 30, 35, 40, 50, 60 mg) showed that the percentage of patients on each prednisone starting dose category was balanced between each of the treatment groups.

Concomitant treatment for GCA

Concomitant treatments for GCA (other than blinded study treatment) as determined by the investigator were reported for 67% of patients in the TCZ QW and TCZ Q2W groups, 78% of patients in the PBO + 26 wk group and 71% of patients in the PBO + 52 wk group. Steroids (including low-dose glucocorticoid treatment) were the most commonly reported concomitant treatments for GCA.

Antimetabolites (methotrexate) were received by 11% of patients in the TCZ QW group, 10% of patients in the TCZ Q2W group, 16% of patients in the PBO + 26 wk group and 18% of patients in the PBO + 52 wk group.

Salicylates (aspirin) were taken by 18% of patients in the TCZ QW, TCZ Q2W and PBO + 26 wk groups and 16% of patients in the PBO + 52 wk group while analgesics (mainly paracetamol) were taken by 3% of patients in the TCZ QW group, 14% of patients in the TCZ Q2W group, 16% of patients in the PBO + 26 wk group and 12% of patients in the PBO + 52 wk group.

Numbers analysed

Of the 251 patients randomized into the study (100 patients to the TCZ QW group, 50 patients to the TCZ Q2W group, 50 patients to the PBO + 26 wk group and 51 patients to the PBO + 52 wk group), 250 patients received the treatment to which they were assigned. One patient (255730/11341) who was randomized to the TCZ Q2W group withdrew the same day they were randomized and did not receive any study treatment. This patient was excluded from the safety and intent-to-treat (ITT) efficacy analysis populations

Table 9 - Overview of analysis population (all patients)

Analysis Populations
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper	PBO QW + 52 Week Prednisone Taper	TCZ QW + 26 Week Prednisone Taper	TCZ Q2W + 26 Week Prednisone Taper
All Patients Population	50	51	100	50
Intent-to-Treat Population	50	51	100	49
Pt did not receive any study drug	0	0	0	1
Safety Evaluated Population	50	51	100	49
Pt did not receive any study drug	0	0	0	1
Randomized Population	50	51	100	50

Number of patients for each population based on the corresponding Planned or Actual treatment group.
The counts for patients who did not receive any study drug are based on the Planned treatment group.

Program: /opt/BIOSTAT/prod/cnl1935e/i28119a/t_pop.sas / Output:
/opt/BIOSTAT/prod/cnl1935e/i28119a/reports/t_pop_AP.out (PDRD) 11JUL2016 21:35 Page 1 of 1

Outcomes and estimation

Table 10 - Overview of efficacy (ITT population)

Primary Endpoint: Proportion of Patients Achieving Sustained Remission at Week 52			
	PBO QW + 26 Week Prednisone Taper N = 50	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
Responders	7 (14.0%)	56 (56.0%)	26 (53.1%)
Difference in response rates (99.5% CI)		42.00 (18.00, 66.00)	39.06 (12.46, 65.66)
p-value [a]		< 0.0001	< 0.0001
Sensitivity analysis: excluding the requirement of normalized CRP(< 1 mg/dL) from the definition of sustained remission			
Responders	10 (20.0%)	59 (59.0%)	27 (55.1%)
Difference in response rates (99.5% CI)		39.00 (14.77, 63.23)	35.10 (7.80, 62.40)
p-value [a]		< 0.0001	0.0004
Sensitivity analysis: Regardless of Adherence to Prednisone Taper Regimen			
Responders	7 (14.0%)	59 (59.0%)	26 (53.1%)
Difference in response rates (99.5% CI)		45.00 (20.87, 69.13)	39.06 (12.46, 65.66)
p-value [a]		< 0.0001	< 0.0001
Sensitivity analysis: Completers Compliant with Study Medication			
Responders	4 (14.8%)	29 (64.4%)	15 (62.5%)
Difference in response rates (99.5% CI)		49.63 (15.58, 83.68)	47.69 (9.61, 85.76)
p-value [a]		< 0.0001	0.0005
Key Secondary Endpoint: Proportion of Patients Achieving Sustained Remission at Week 52			
	PBO QW + 52 Week Prednisone Taper N = 51	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
Responders	9 (17.6%)	56 (56.0%)	26 (53.1%)
Difference in response rates (99.5% CI)		38.35 (17.89, 58.81)	35.41 (10.41, 60.41)
p-value [a]		< 0.0001	0.0002
Sensitivity analysis: excluding the requirement of normalized CRP (< 1 mg/dL) from the definition of sustained remission			
Responders	17 (33.3%)	59 (59.0%)	27 (55.1%)
Difference in response rates (99.5% CI)		25.67 (2.56, 48.77)	21.77 (-5.46, 48.99)
p-value [a]		0.0030	0.0292
Sensitivity analysis: Regardless of Adherence to Prednisone Taper Regimen			
Responders	9 (17.6%)	59 (59.0%)	26 (53.1%)
Difference in response rates (99.5% CI)		41.35 (20.98, 61.73)	35.41 (10.41, 60.41)
p-value [a]		< 0.0001	0.0002
Sensitivity analysis: Completers Compliant with Study Medication			
Responders	6 (26.1%)	29 (64.4%)	15 (62.5%)
Difference in response rates (99.5% CI)		38.36 (5.77, 70.94)	36.41 (-1.40, 74.23)
p-value [a]		0.0035	0.0127

Other Secondary Efficacy Endpoints at Week 52				
	PBO QW + 26 Week Prednisone Taper N = 50	PBO QW + 52 Week Prednisone Taper N = 51	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
Time to First GCA Disease Flare				
Patient with event (%)	34 (68%)	25 (49%)	23 (23%)	13 (26.5%)
Median TTE (days) (range)	165 (1 - 365)	295 (1 - 362)	NE (1 - 367)	NE (1 - 364)
HR (99% CI) (vs PBO + 26 week taper)			0.23 (0.11, 0.46)	0.28 (0.12, 0.66)
Stratified p-value [b]			**<0.0001**	**0.0001**
HR (99% CI) (vs PBO + 52 week taper)			0.39 (0.18, 0.82)	0.48 (0.20, 1.16)
Stratified p-value [b]			**0.0011**	0.0316
Actual Cumulative Prednisone Dose (mg)				
Median (95% CI)	3296 (2730, 4024)	3818 (2818, 4426)	1862 (1582, 1942)	1862 (1568, 2240)
P-value [c] (vs PBO + 26 week taper)			**<0.0001**	**0.0003**
P-value [c] (vs PBO + 52 week taper)			**<0.0001**	**<0.0001**

CRP, C-reactive protein; CI, Confidence Interval; HR, Hazard Ratio; NE, not evaluable; PBO, placebo; QW, weekly; Q2W, every 2 weeks; TCZ, tocilizumab; TTE, time to event.

[a] P-value calculated using Cochran-Mantel-Haenszel method

[b] Cox proportional hazards model adjusting for stratification factor of starting prednisone dose (≤ 30 mg/day, >30 mg/day).

[c] P-value calculated using Van Elteren's test.

Source: t_ef_sum_IT; t_ef_sum_IT_NAPR; t_ef_sum_IT_NATAP; t_ef_sum_ITCSCT; t_fl_km_IT; t_ex_cumvelt_IT.

Significance level for primary endpoints: 0.005

Superiority of both the TCZ QW and TCZ Q2W dose groups compared to placebo when combined with a 26-week prednisone taper was demonstrated with regard to the primary efficacy endpoint, the proportion of patients achieving sustained remission at Week 52, following induction and adherence to the protocol-defined prednisone taper.

A tipping point analysis was performed where escape patients and patients with GCA flare prior to withdrawal were classed as non-responders. All other withdrawals (2 in PBO group, 14 in TCZ QW, 5 in TCZ Q2W) were subsequently classed as either non-responder or responder and change in the primary endpoint was investigated. No tipping point was observed with increasing number of withdrawals classed as responders.

A post-hoc analysis of the individual criteria of the composite endpoint of sustained remission was performed. In this analysis, the percentage of patients meeting each individual criterion for not achieving sustained remission was determined. Results showed that higher proportions of patients flared and subsequently received treatment with escape prednisone in the placebo groups compared to the TCZ groups.

Table 11 - Summary of components of sustained remission (ITT population)

Category	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Received Escape Therapy, n(%)	37 (74.0%)	28 (54.9%)	23 (23.0%)	16 (32.7%)
First Flare of any type, n(%)	36 (72.0%)	29 (56.9%)	27 (27.0%)	17 (34.7%)
First flare with SnS and ESR elevation, n(%)	19 (38.0%)	19 (37.3%)	0	3 (6.1%)
First flare with SnS only, n(%)	11 (22.0%)	8 (15.7%)	25 (25.0%)	14 (28.6%)
First flare with ESR elevation only, n(%)	6 (12.0%)	2 (3.9%)	1 (1.0%)	0
Withdrawal from study prior to Week 52, n(%)	6 (12.0%)	5 (9.8%)	15 (15.0%)	8 (16.3%)
Elevated CRP without flare, n(%)	26 (52.0%)	31 (60.8%)	5 (5.0%)	3 (6.1%)
Received additional prednisone, including escape n(%)	36 (72.0%)	27 (52.9%)	26 (26.0%)	16 (32.7%)

SnS stands for Signs and Symptoms recorded on the GCA assessment eCRF.
Patients who received Escape medication will be classed as non-responders.
Flare with SnS only is a flare for which at least one sign or symptom was observed and no ESR elevations attributed to GCA were observed.
Flare with ESR elevation only is a flare for which no other sign or symptom was observed other that ESR attributed to GCA.
Patients who withdraw prior to week 52 will be classed as non-responders.
Patients who have elevated CRP (>1 mg/dL) at Week 12 or later, and their next CRP value is also elevated or is missing and they have not flared at that visit will be counted in the "Elevated CRP without flare" category.
Patients who did not adhere to the protocol-defined prednisone taper by receiving more than 100mg additional steroid from Week 12 to Week 52 will be classed as non-responders.
Categories are not mutually exclusive.
Only a patients first flare is summarised as this is when escape should have been initiated.

Program: /opt/BIOSTAT/prod/cnl1935e/i28119a/t_srem_comp_ahl36.sas
Output: /opt/BIOSTAT/prod/cnl1935e/i28119a/reports/t_srem_comp_ahl36_IT.out
20SEP2016 16:29 Page 1 of 1

Page 1 of 1

Evaluation of signs and symptoms present at the time of first GCA flare showed that the majority of patients in the TCZ groups presented with clinical signs and symptoms in the absence of elevated ESR attributed to GCA. In contrast, the placebo patients were reported with flares due to clinical signs and symptoms both in the presence and absence of an elevated ESR attributable to GCA. Eight first flares due to an elevated ESR in the absence of clinical GCA signs and symptoms were reported in the placebo groups compared to one such flare in the TCZ QW group only.

Elevated CRP without flare includes all patients who had two consecutive CRP elevations between Week 12 and Week 52. Consecutive CRP elevations (without flare) were reported in higher proportions of patients in the placebo groups (PBO + 26 wk: 52.0%; PBO + 52 wk: 60.8%) compared to the TCZ groups (TCZ QW: 5.0%; TCZ Q2W: 6.1%). The majority of CRP elevations were in those patients classed as non-responders due to reporting a GCA flare, having received treatment with escape prednisone or being unable to adhere to the protocol defined prednisone taper. Fifteen of the patients with CRP elevations represent those who had not reported a flare, had not received treatment with escape prednisone and had adhered to the protocol defined prednisone taper, i.e. the two consecutive elevated CRP elevations was the only component of the remission definition that rendered these patients non-responders. A sensitivity analysis that classed these fifteen patients as responders still showed superiority of the two TCZ doses over PBO + 26 wk.

There were three patients in the TCZ QW group who received > 100 mg additional prednisone from Week 12 to Week 52 (including all escape therapy, commercial prednisone and taper prednisone [both open-label and blinded taper]). One patient in each of the placebo groups moved onto escape prednisone but did not receive >100 mg treatment. A sensitivity analysis that classed the three patients with >100 mg additional prednisone as non-responders still showed superiority of the two TCZ doses over PBO + 26 wk.

Key secondary efficacy endpoint

The key secondary efficacy endpoint was the proportion of patients in sustained remission at Week 52 in the TCZ groups in combination with a 26-week prednisone taper compared with placebo in combination with a 52-week prednisone taper.

Both the TCZ QW and TCZ Q2W dose groups met non-inferiority and in post hoc analyses subsequently superiority to placebo with regard to the key secondary endpoint.

The subsequent CMH superiority analysis, which was added post-hoc, yielded p-values of < 0.0001 for the TCZ QW group and 0.0002 for the TCZ Q2W group versus placebo which indicated that not only was TCZ combined with a 26-week prednisone taper non-inferior to placebo when combined with a 52-week prednisone taper but the difference in response rates met the criteria for statistical superiority of TCZ over placebo for both dose groups.

Superiority of the TCZ QW dose group to the 52-week prednisone only control group was confirmed in all sensitivity analyses. Superiority of the TCZ Q2W arm to PBO + 52 wk was also confirmed in the sensitivity analysis that included all subjects regardless of adherence to the prednisone taper. The TCZ Q2W arm met non-inferiority for both the sensitivity analysis excluding the requirement of normalized CRP (< 1 mg/dL) from the definition of remission and the analysis of completers adhering to study medication, but could not show superiority in these analyses.

Secondary efficacy endpoints

All other secondary endpoints were tested at a type I error level of 1% but were not part of the confirmatory testing sequence and not subject to multiplicity control. Hence, results are not confirmatory.

- Time to first GCA disease flare after clinical remission (up to 52 weeks)

Time to event analysis (stratified by starting prednisone dose) revealed a statistically significantly lower risk of GCA disease flare in both TCZ groups compared to the 26-week prednisone only control group. Analysis comparing the TCZ groups to the 52-week prednisone only control group showed a statistically significant lower risk of disease flare in the TCZ QW group, whereas the numerical improvement achieved in the TCZ Q2W group did not reach the pre-specified threshold for statistical significance (p < 0.01 defined for other secondary endpoints).

- Summary of total cumulative prednisone dose over 52 weeks

Expected cumulative prednisone dose to Week 52 was calculated based on a patient's starting prednisone dose, the taper schedule (26-week or 52-week taper), and the assumption that the patient continued the taper without error.

Median expected cumulative prednisone dose was, therefore, similar in the TCZ QW (1337.0 mg), TCZ Q2W (1442.0 mg), and PBO + 26 wk (1337.0 mg) groups and higher in the PBO + 52 wk (2607.5 mg) group. Median actual cumulative prednisone dose to Week 52 (including all taper prednisone [both open-label and blinded taper]; escape therapy and commercial concomitant prednisone) was 1862.0 mg in both of the TCZ QW and TCZ Q2W treatment groups compared with 3296.0 mg in the PBO + 26 wk group and 3817.5 mg in the PBO + 52 wk group. The associated stratified analysis p-values for TCZ versus placebo in combination with a 26-week prednisone taper were p < 0.0001 for the TCZ QW group and p = 0.0003 for the TCZ Q2W group, indicating a statistically significantly lower cumulative prednisone dose to Week 52 in both the TCZ QW and TCZ Q2W treatment groups when compared to placebo in combination with a 26 week prednisone taper period.

Corresponding stratified analysis p-values for the TCZ QW and TCZ Q2W groups versus placebo in combination with a 52-week prednisone taper were both p < 0.0001, indicating a statistically significantly lower cumulative prednisone dose to Week 52 in both the TCZ QW and TCZ Q2W treatment groups compared to placebo in combination with a 52 week prednisone taper.

Of note, actual prednisone doses were much higher in all 4 study arms than expected (based on the individual taper regimen). Median expected cumulative prednisone doses were 1337.00 (PBO + 26 wk), 2607.50 (PBO + 52 wk), 1337.00 (TCZ QW), and 1442.00 (TCZ Q2W) .

- Change from baseline in SF-36 (Physical and Mental Component Summaries) at 52 weeks

The increased change from baseline to Week 52 for the SF-36 Mental Component Score showed a numeric improvement in all treatment groups, placebo and TCZ). Comparison of TCZ to prednisone taper showed a numerical benefit of TCZ QW compared to PBO + 26 wk (0.61, 99% CI: -5.86,7.07) and PBO + 52 wk (4.44, 99% CI: -0.69,9.56); A numerical benefit pf TCZ Q2W was observed in comparison to PBO + 52 wk (3.27, 99% CI: -2.59,9.14), while a numerical disadvantage over PBO + 26 wk was observed (-0.56, 99% CI: -7.64,6.53).

For the SF-36 Physical Component Score, the change from baseline to Week 52 showed a numeric improvement in both of the TCZ groups, while both placebo groups showed a slight worsening in PCS. Comparing treatment arms, only the difference observed in the TCZ QW group compared to the PBO + 52 wk group was statistically significant at the 0.01 significance level (p = 0.0024). All other comparisons only showed a numerical benefit of TCZ arms.

- Change from baseline in PGA of disease activity (VAS scale) at 52 weeks

The patient global VAS item rates patients' assessment of the effect of their GCA at the present time. A decline from baseline score (negative change) indicates improvement.

All treatment groups (placebo and TCZ) showed a decline from baseline in patient's global VAS scores. The TCZ Q2W group demonstrated a statistically significant improvement over the PBO + 26 wk group (p = 0.0059) and PBO + 52 wk group (p = 0.0081). While not statistically significant at the pre-specified level of 0.01, for the TCZ QW group, the mean change from baseline scores was numerically lower in the TCZ QW group than both PBO groups. A post-hoc sensitivity analysis of the change from baseline to Week 52 in Patient's Global VAS based on observed data only (where post-escape PGA VAS data were included in the analysis and not considered as missing) again showed a statistically significant improvement for the TCZ Q2W group over both the PBO + 26 wk group (p = 0.0091) and PBO + 52 wk group (p = 0.0027) and a numerical improvement in mean change from baseline scores for the TCZ QW group compared with both PBO groups, although neither reached statistical significance at the pre-specified level of 0.01.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12 - Summary of Efficacy for trial WA2819

Title: A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in subjects with giant cell arteritis.		
Study identifier	WA28119	
Design	Multicenter, randomized, placebo-controlled, double-blind, 4 armed parallel group trial. The study includes a 52-week blinded period (Part 1); 104-week open-label extension/long-term follow up (Part 2) is not part of this MAA.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable not applicable
Hypothesis	Superiority (Primary endpoint), Non-inferiority (Secondary endpoint)	
Treatments groups	PBO + 26 wk	Placebo SC QW + 26 week prednisone taper, 52 weeks, n = 50

	PBO + 52 wk		Placebo SC QW + 52 week prednisone taper, 52 weeks, n = 51
	TCZ QW + 26 wk		TCZ 162mg QW + 26 week prednisone taper, 52 weeks, n = 100
	TCZ Q2W + 26 wk		TCZ 162mg Q2W + 26 week prednisone taper, 52 weeks, n = 50
Endpoints and definitions	Primary endpoint	Sustained Remission	Proportion of patients in sustained remission at week 52
	Key Secondary endpoint	Sustained Remission	Proportion of patients in sustained remission at week 52
Database lock	Unknown.		

Results and Analysis

Analysis description	**Primary Analysis (Superiority over PBO + 26 wk)**			
Analysis population and time point description	ITT set (patients with at least one dose of TCZ/placebo) at 52 weeks			
Descriptive statistics and estimate variability	Treatment group	PBO + 26 wk	TCZ QW + 26 wk	TCZ Q2W + 26 wk
	Number of subject	50	100	49
	Sustained Remission (n %)	7 (14.0%)	56 (56.0%)	26 (53.1%)

Effect estimate per comparison	Sustained Remission	Comparison groups	TCZ QW + 26 wk vs. PBO + 26 wk
		Difference	42.00
		99.5% CI	(18.00, 66.00)
		P-value	< 0.0001
	Sustained Remission	Comparison groups	TCZ Q2W + 26 wk vs. PBO + 26 wk
		Difference	39.06
		99.5% CI	(12.46, 65.66)
		P-value	< 0.0001
Notes	Both TCZ groups were statistically significant superior to placebo with 26 week taper regimen on an overall significance level of 1% (0.5% per comparison).		

Analysis description	**Key Secondary Analysis (Non-inferiority compared to PBO + 52 wk)**			
Analysis population and time point description	ITT set (patients with at least one dose of TCZ/placebo) at 52 weeks			
Descriptive statistics and estimate variability	Treatment group	PBO + 52 wk	TCZ QW + 26 wk	TCZ Q2W + 26 wk
	Number of subject	51	100	49
	Sustained Remission (n %)	9 (17.6%)	56 (56.0%)	26 (53.1%)

Effect estimate per comparison	Sustained Remission	Comparison groups	TCZ QW + 26 wk vs. PBO + 52 wk
		Difference	38.35
		99.5% CI	(17.89, 58.81)
		NI-margin	-22.5
	Sustained Remission	Comparison groups	TCZ Q2W + 26 wk vs. PBO + 52 wk
		Difference	35.41
		99.5% CI	(10.41, 60.41)
		NI-margin	-22.5

Notes	Superiority of TCZ over PBO + 52 wk tapering was analysed post-hoc. Both TCZ arms had significantly higher response rates ($p < 0.0001$ and $p = 0.0002$, respectively) with an overall significance level of 1% (0.5% per comparison).

Analysis performed across trials (pooled analyses and meta-analysis)

Analyses across trials were not performed.

Clinical studies in special populations

No dedicated studies in special population were performed in context of the development in GCA.

Supportive studies

Long term extension WA28119

Part 2 of the study WA28119 (presented as main study above) is an ongoing 104-week open-label extension/ long-term follow up phase, ending at Week 156. The purpose of Part 2 is to assess the long-term safety and maintenance of efficacy after 52 weeks of therapy with TCZ, to explore the rate of relapse and the requirement for TCZ therapy beyond 52 weeks, and to gain insight into the potential long-term steroid sparing effect of TCZ.

Use of SC open-label TCZ at the Week 52 visit was dependent on the remission status of the patient at that visit. If a patient was in remission their TCZ/placebo SC injections were stopped and they were observed in the absence of further TCZ treatment. If a patient was not in remission at the Week 52 visit or if a patient relapsed/flared at any time during Part 2, they could receive SC open-label TCZ QW at the discretion of the investigator, regardless of their allocated treatment regime in Part 1 of the study (to which the investigator remained blinded). Treatment with glucocorticoids and methotrexate are permitted at any time during Part 2 at a dose and duration chosen by the investigator. As in Part 1 of the study, GCA flare was determined by the investigator and was based on the assessment of clinical signs and symptoms and ESR elevations attributed to GCA. The sites remained blinded to the CRP levels during Part 2 of the study.

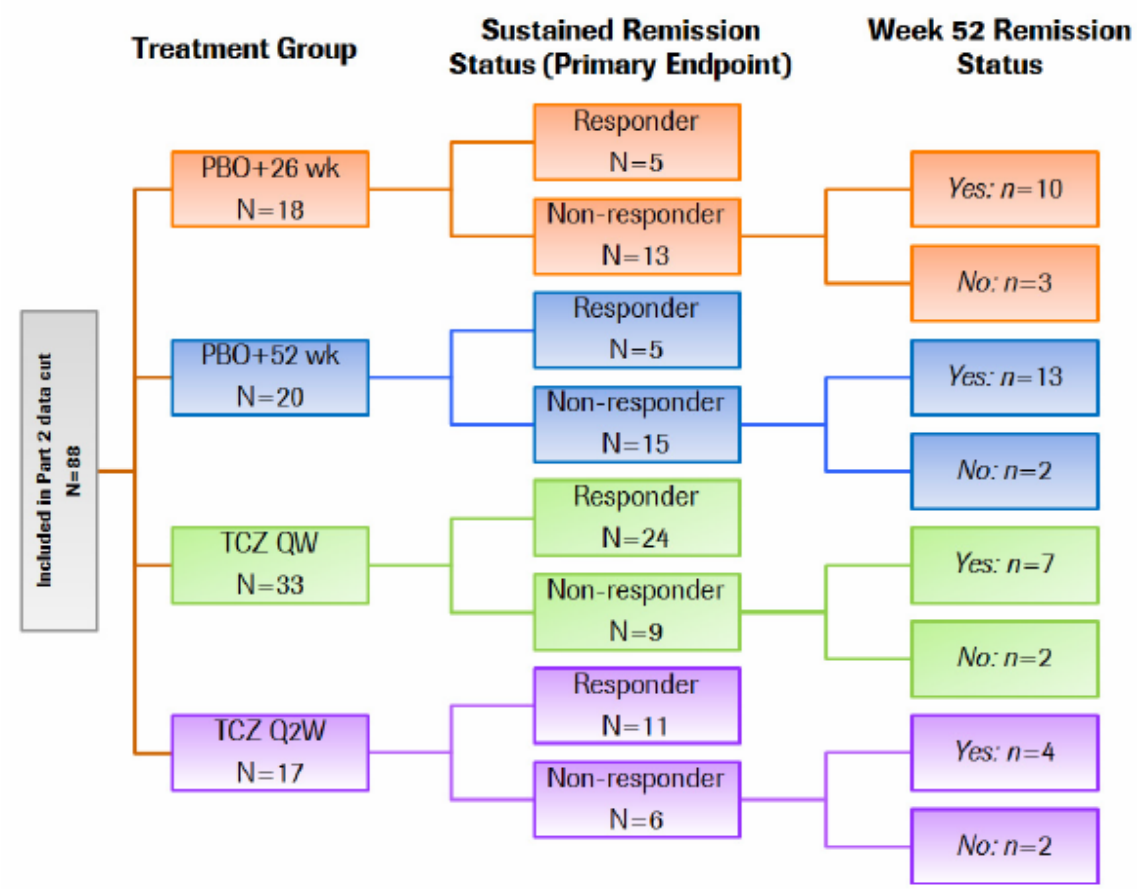
Patient data were treated and subsequently analysed based on response to treatment in Part 1 of the study. In Part 1, 88 responders (those who met the primary endpoint) were followed off TCZ treatment to assess the maintenance of response enabled by one year of TCZ treatment. Part 1 non-responders were analysed to determine whether they can attain remission following treatment with open-label TCZ QW during Part 2 of the study. Both groups were evaluated to assess the effectiveness of open-label TCZ QW treatment in bringing about remission following a GCA flare.

Patient flow

At the time of the Part 1 data cut-off (11 April 2016), there were 88 patients who had reached the Week 100 visit or beyond, with some patients having participated up to Week 136. Data for patients who did not reach the Week 100 visit due to withdrawal from the study or death during Part 2 are also included in the analysis.

Of the 88 patients evaluated at the time of the data cut (see figure 11), 45 met the primary endpoint during Part 1 of the study (i.e., were in sustained remission from Week 12 to Week 52; 5 in each of the PBO groups, 24 in the TCZ QW group and 11 in the TCZ Q2W arm). Of the remaining 43 patients who were non-responders in Part 1 of the study, 34 were in remission at the Week 52 visit due to treatment with escape prednisone. The remaining nine patients were not in remission at the Week 52 visit.

Figure 11 - Disposition of Part 2 patients



Treatment at week 52

Upon entering Part 2 of the study, 43 of the 45 patients who met the primary endpoint in Part 1 stopped their TCZ/placebo injections and were followed up off TCZ treatment; erroneously, one patient each from the TCZ QW and PBO + 52 wk groups started open-label TCZ (in the absence of glucocorticoids) at the Week 52 visit despite being in remission. Six patients received treatment other than or in addition to open label TCZ at the Week 52 visit: three received glucocorticoids alone, one received glucocorticoids plus MTX and two received MTX alone.

The 34 patients who were non-responders in Part 1 of the study and were in remission at Week 52 were either followed up off treatment or received treatment with open-label TCZ and/or glucocorticoids and/or MTX.

The nine patients who were non-responders in Part 1 of the study and were not in remission at Week 52 were treated with open-label TCZ and/or glucocorticoids and/or MTX.

Efficacy results

Part 1 Responders: Maintenance of Response in Part 2

Table 13 - Part 1 responders: Patients who flared during Part 2

Part 1 Treatment group	n	Patients with Flares (%)	Patients without Flares (%)
PBO + 26 wk	5	1 (20%)	4 (80%)
PBO + 52 wk	5	1 (20%)	4 (80%)
TCZ QW	24	8 (33%)	16 (67%)
TCZ Q2W	11	8 (73%)	3 (27%)

Two patients (Patients 255202/10062 and 253755/10262) were receiving treatment for their GCA at the time of first flare in Part 2; both patients were from the original TCZ QW group and were receiving 5 mg/day glucocorticoids, one (Patient 253755/10262) in combination with 15 mg MTX QW.

Two patients (255228/10484 and 255207/10041) flared within two weeks of entering Part 2, but the majority of relapses occurred at least 12 weeks after the discontinuation of TCZ/placebo injections at Week 52 There was no pattern to the timing of flares during Part 2.

Part 1 Non-responders: Relapses in Part 2

Table 14 - Part 1 non-responders: Patients who flared during Part 2

Subgroup	n	Part 1 Treatment Group	n	Patients who flared in Part 2 (%)	Patients who did not flare in Part 2 (%)
Part 1 Non-responders: in Remission at Week 52	34	PBO + 26 wk	10*	3 (30%)	7 (70%)
		PBO + 52 wk	13	6 (46%)	7 (54%)
		TCZ QW	7	6 (86%)	1 (14%)
		TCZ Q2W	4	4 (100%)	0
Part 1 non-Responders: Not in Remission at Week 52	9	PBO + 26 wk	3	0	3 (100%)
		PBO + 52 wk	2	2 (100%)	0
		TCZ QW	2	0	2 (100%)
		TCZ Q2W	2	1 (50%)	1 (50%)

PBO = placebo, QW = weekly, Q2W = every other week, wk = week.

* Includes the two patients who did not flare and withdrew from the study.

Relapses on Open-label TCZ

Forty five patients received treatment with open-label TCZ during Part 2 of the study. Eighteen patients started open-label TCZ at Week 52. Twenty-eight patients had a GCA flare in Part 2 that was treated with open-label TCZ. Two patients erroneously started open-label TCZ at study Week 53.

Table 15 - Relapse on open-lablel TCZ in Part 2 of the study

Part 1 treatment group	Patient	Subtype	Part 1 responder?	TCZ Start Day	Day of Relapse	Symptoms at Relapse
PBO + 26	10501	Relapsing	No	365	386	Cranial and PMR
PBO + 52	10343	Relapsing	No	372	547	PMR and myalgia
	10061	Relapsing	No	367	383*	Cranial, blurred vision
	10541	Relapsing	No	379	771	PMR
	10222	Relapsing	No	364	491	Cranial
TCZ QW	10561	Relapsing	No	367	801	PMR
	10241	Relapsing	Yes	449	645*	Cranial
TCZ Q2W	10542	New-onset	No	366	511	PMR
	10922	New-onset	No	365	493 and 669*	Cranial, blurred vision/cranial, PMR, other
	10023	Relapsing	No	479	717*	Cranial and blurred vision
	10224	New-onset	No	468	472*	Cranial and PMR, other

PBO = placebo, PMR = polymyalgia rheumatica, QW = weekly, Q2W = every other week, TCZ = tocilizumab.

* Second relapse in Part 2

Eleven patients (65%) relapsed while receiving treatment with open-label TCZ; ten were non-responders in Part 1 (due to non-adherence to the protocol defined prednisone taper, elevations in CRP or withdrawal from the study) or had flared during Part 1 of the study. Three patients relapsed within a few weeks of starting open-label TCZ, which likely represents inadequate disease control after the initiation of open-label TCZ in Part 2.

Four of the flares were second flares in patients who had initiated open-label TCZ to treat a previous relapse during Part 2. One patient relapsed twice while receiving treatment with open-label TCZ.

Of the 11 patients who relapsed on open-label TCZ during Part 2, six were receiving concomitant treatment with glucocorticoids and one patient was also receiving MTX at the time of flare.

Tocilizumab for induction and maintenance of remission in giant cell arteritis: A Phase 2, randomized, double-blind, placebo-controlled trial (supportive phase II investor-initiated study ML25676)

In this randomized, double-blind, placebo controlled Phase II study the use of IV TCZ in 30 patients aged ≥ 50 years and diagnosed with GCA according to the 1990 ACR criteria (Villiger et al. 2016). Patients with new onset or relapsing disease were randomized (2:1) to receive 8 mg/kg IV TCZ every 4 weeks (Q4W) or placebo over 1 year. Patients received concomitant glucocorticoids (prednisolone), at a starting dose of 1 mg/kg/day and were tapered in a controlled fashion to 0.1 mg/kg/day by Week 12. Subsequently, the daily glucocorticoid dose was further reduced by 1 mg every month.

Efficacy Results

Complete remission by Week 12 was reached in 17/20 (85%) patients treated with TCZ compared to 4/10 (40%) patients treated with placebo (difference [95% CI]: 45% [11%, 79%]; p = 0.0301). Relapse-free

survival was achieved in 17/20 (85%) patients in the TCZ group and 2/10 (20%) patients in the placebo group by Week 52 (difference [95% CI]: 65% [36%, 94%]; p = 0.0010). The mean time difference to stop glucocorticoids was 12 weeks in favour of TCZ (95% CI: 7, 17; p < 0.0001), leading to a weight-adjusted cumulative prednisolone dose of 43 mg/kg (median IQR: 39, 52) in the TCZ group versus 110 mg/kg (median IQR: 88, 150) in the placebo group (p = 0.0005) after 52 weeks.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study WA28119 is a Phase III, multicentre, randomized, placebo controlled, double-blind, parallel group superiority trial in patients with GCA designed to evaluate the safety and efficacy of TCZ for the treatment of GCA. The study includes a 52-week blinded period (Part 1) followed by a 104-week open-label period (Part 2), with a total duration of the study of 156 weeks.

The target population for this study were adult patients with GCA who have active disease (signs and symptoms and elevated ESR) within the 6 weeks prior to baseline visit. Because the Sponsor anticipated that the vast majority of subjects enrolled to WA28119 would meet the ACR 1990 classification criteria for the diagnosis of GCA, the inclusion criteria were broadly based around these criteria. However, since much progress has been made in understanding the clinical presentation and pathology of the disease since 1990 the sponsor modified these criteria. New vascular imaging modalities having all emerged and altered the approach to diagnosing GCA, therefore, revised diagnostic criteria were used that are consistent with current clinical practice. These inclusion criteria that consider a broader array of cranial symptoms that occur in GCA beyond headache alone (e.g., jaw claudication, scalp tenderness, ischemia-related vision loss); PMR symptoms occurring in the setting of GCA proven by either biopsy or imaging; and evidence of large vessel vasculitis in cross-sectional imaging (MRA, CTA, PET-CT, or angiography), none of which were included in the 1990 criteria. This approach is considered acceptable by CHMP.

Patients were screened up to 6 weeks (42 days) prior to the baseline randomization visit. During the screening period, patients could receive glucocorticoids for the treatment of GCA at the discretion of the investigator. By the end of the screening period patients had to switch to the Sponsor-provided prednisone in order to follow the protocol-defined prednisone taper in combination with either placebo or two different TCZ regimens. Patients were randomized in a 1:1:2:1 ratio into four groups: Placebo SC weekly (QW) + 26-week prednisone taper regimen (PBO + 26 wk; n = 50); Placebo SC QW + 52-week prednisone taper regimen (PBO + 52 wk; n = 51), 162 mg TCZ SC QW + 26-week prednisone taper regimen (TCZ QW; n = 100)and 162 mg TCZ SC every other week (Q2W) + 26-week prednisone taper regimen (TCZ Q2W; n = 50). The corner stone of management of GCA is immediate initiation of treatment (i.e. high-dose glucocorticosteroide treatment) after clinical suspicion of GCA is raised in order to prevent further visual loss and other ischaemic complications. It is further recommend to maintain the initial high dose for a month and taper gradually thereafter (BSR and BHPR Guidelines for the management of giant cell arteritis: doi:10.1093/rheumatology/keq039b; EULAR recommendations for the management of large vessel vasculitis Ann Rheum Dis 2009;68:318-323 doi:10.1136/ard.2008.088351). Improvement of symptoms is typical expected within 72 hours after initiation of standard therapy. However, TCZ was initiated up to 42 days (6 weeks) after initiation of treatment for GCA; in parallel the prednisone taper regimen was started.

The primary objective of the study was to evaluate the efficacy of TCZ compared to placebo, in combination with a 26-week prednisone taper regimen. Therefore the MAH implemented the requirement “induction of remission within 12 weeks of randomisation”, thus remission was investigated max 18 weeks after (suspected) onset of GCA. For the purpose to evaluate the primary study endpoint this approach is

acceptable. Unfortunately the design of study WA28119 does not allow to directly assessing the question of early disease control; it rather enables to evaluate TCZ supporting the prednisone tapering regimen.

It is acknowledged that early disease control in GCA is important – a fact that is reinforced by way of treatment guidelines stating that high-dose glucocorticoid therapy should be initiated immediately upon clinical suspicion of GCA (Warrington and Matteson, 2007; Dasgupta et al, 2010). However, despite the rapidity of the initial response, the majority of patients relapse either during tapering or after complete withdrawal of glucocorticoids (Martinez-Lado et al 2011; Andersson et al 1986; Proven et al 2003; Alba et al 2014). Therefore, there is still an unmet need in identifying an agent capable of maintaining disease remission during glucocorticoid tapering, particularly when daily doses begin to reach levels at which patients typically experience disease relapse.

Data from the WA28119 study demonstrate a superior treatment effect of TCZ at 52 weeks, but also show an impact on treatment response as early as Week 1 after initiation of TCZ treatment. Thus, the differences in efficacy across groups were present at the earliest possible time points for assessment. These exploratory findings provide evidence on the efficacy of TCZ in establishing early disease control, even though this was not the principal aim of study WA28119.

The primary efficacy endpoint is the proportion of patients in sustained remission at Week 52 treated with TCZ (QW or Q2W) or placebo in combination with 26 weeks prednisone taper regimen. The key secondary efficacy endpoint was the proportion of patients in sustained remission at Week 52 treated with TCZ (QW or Q2W) or placebo in combination with 52 weeks prednisone taper regimen. Both endpoints are considered acceptable.

Efficacy data and additional analyses

A total of 251 patients were enrolled into the study (100 patients to the TCZ QW group, 50 patients to the TCZ Q2W group, 50 patients to the PBO + 26 wk group and 51 patients to the PBO + 52 wk group), 250 patients received the treatment to which they were assigned. GCA disease characteristics were well balanced between the treatment groups.

The efficacy data are based on the primary analysis, which was conducted after all patients had completed the double-blind treatment period (i.e., 52 weeks of study treatment unless the patient was prematurely withdrawn). Patients who flared and received escape therapy, who did not adhere to the prednisone taper regimen (i.e., were given more than 100 mg additional glucocorticoids), who had two consecutive CRP elevations ($\geq$ 1 mg/dL) between Weeks 12 and 52, who withdrew from the study prior to Week 52, or for whom a remission status could not be determined at Week 52, were classed as non-responders in the primary analysis.

The primary endpoint, superiority of each of the TCZ arms (with 26 week prednisone tapering) over PBO with 26 week tapering, was met. Sustained remission at Week 52 was achieved in 56.0% of patients in the TCZ QW group, 53.1% of patients in the TCZ Q2W group and 14.0% of patients in the PBO + 26 wk group. The difference in the percentage of responders between the TCZ QW group and placebo was 42.0% (99.5% CI: 18.0 to 66.0), with an associated p-value of < 0.0001. The difference in the percentage of responders between the TCZ Q2W dose group and placebo was 39.1% (99.5% CI: 12.5 to 65.7), with a p-value of < 0.0001.

The key secondary efficacy endpoint was the proportion of patients in sustained remission at Week 52 in the TCZ groups in combination with a 26-week prednisone taper compared with placebo in combination with a 52-week prednisone taper. Both the TCZ QW and TCZ Q2W dose groups met non-inferiority. In post hoc analyses subsequently superiority to placebo was shown with regard to the key secondary endpoint. Sustained remission at Week 52 was achieved by 56.0% of patients in the TCZ QW group, 53.1% of patients

in the TCZ Q2W group and 17.6% of patients in the PBO + 52 wk group. The difference in the percentage of responders in the TCZ QW group versus the PBO + 52 wk group was 38.4% (99.5% CI: 17.9 to 58.8) and the difference in the percentage of responders in the TCZ Q2W group versus the PBO + 52 wk group was 35.4% (99.5% CI: 10.4 to 60.4). The lower boundaries of the 99.5% CIs for both TCZ dose groups were greater than the non-inferiority margin of -22.5%, meeting the criteria for non-inferiority. Of note, the non-inferiority analysis was not planned in the protocol. The margin was derived in the SAP based on a single study only. Clinical grounds for the margin were not specified.

Superiority of the TCZ QW dose group to the 52-week prednisone only control group was confirmed in all sensitivity analyses, but not for the TCZ Q2W group, which failed to show significant superiority in some of the sensitivity analyses.

Although the median cumulative prednisone dose to Week 52 was higher than expected in all groups, a statistically significantly lower cumulative prednisone dose to Week 52 in both the TCZ QW and TCZ Q2W treatment groups in combination with a 26 week prednisone taper period when compared to placebo was reported. Median actual cumulative prednisone dose to Week 52 (including all taper prednisone [both open-label and blinded taper]; escape therapy and commercial concomitant prednisone) was 1862.0 mg in both of the TCZ QW and TCZ Q2W treatment groups compared with 3296.0 mg in the PBO + 26 wk group and 3817.5 mg in the PBO + 52 wk group. The associated stratified analysis p-values for TCZ versus placebo in combination with a 26-week prednisone taper were $p < 0.0001$ for the TCZ QW group and $p = 0.0003$ for the TCZ Q2W group. The significant lower cumulative prednisone dose to Week 52 in both TCZ groups as compared to the placebo groups might have contributed to the more favourable safety profile under TCZ treatment compared to placebo.

Data from the LTE part of study WA28119 are available for 88 patients, followed up to 136 weeks. Of these 43 of the 45 patients who met the primary endpoint in Part 1, stopped their TCZ/placebo injections and were followed up off TCZ treatment. Of the 45 patients who met the primary endpoint in Part 1 of the study, 27 remained in remission throughout available follow up during Part 2. GCA flares were observed in 18 patients; 1/5 from the PBO + 26 wk group (20%), 1/5 from the PBO + 52 wk group (20%), 8/24 from the TCZ QW group (33%), and 8/11 from the TCZ Q2W group (73%).

These data suggest that in the TCZ groups a higher incidence of flares was observed after stopped their TCZ treatment at 52 weeks than in the placebo groups. However, since the study is still ongoing and these interim data are derived from small patient groups, a firm conclusion cannot be drawn at this point in time. However a rebound after TCZ discontinuation cannot be totally excluded.

The final WA28119 study report will be submitted by Q4 2018, where a possible rebound effect can be further re-assessed based on new data. This long term data will allow a proper assessment of the long-term efficacy i.e. maintenance of efficacy and safety. The MAH has committed to state the lack of data in the RMP under missing information. The final CSR and updated RMP will be submitted by Q1 2019.

Additional evidence for efficacy of TCZ in the treatment of GCA was provided from the data of the investigator-initiated, randomized, double-blind, placebo controlled Phase II study ML25676. Patients aged > 50 years with new onset or relapsing GCA (according to the 1990 ACR criteria) (Villiger et al. 2016) were randomized (2:1) to receive 8 mg/kg IV TCZ every 4 weeks (Q4W) or placebo over 1 year. Patients received concomitant glucocorticoids (prednisolone), at a starting dose of 1 mg/kg/day and were tapered in a controlled fashion to 0.1 mg/kg/day by Week 12. Subsequently, the daily glucocorticoid dose was further reduced by 1 mg every month. The study showed a statistically significant difference in the proportion of TCZ-treated patients achieving complete remission at Week 12 (primary endpoint) compared to those receiving glucocorticoids alone (TCZ plus glucocorticoids: 85% [17/20]; placebo plus glucocorticoids: 40% [4/10]). There was also a statistically significant difference in the proportion of patients that were relapse-free at Week 52 in the TCZ group in comparison to the placebo group as well as a significant reduction in the cumulative weight-adjusted prednisolone dose between the TCZ and placebo groups.

Although the design of this trial was more suitable to evaluate the effect on TCZ on the entire course of GCA, especially the effect on timely disease control, these data are only supportive since the TCZ dose and route of administration (8 mg/kg IV Q4W) differ from the claimed dosage. Moreover the provided data (publication) do not allow an in-depth assessment.

Conclusions on the clinical efficacy

Study WA28119 met its primary and key secondary endpoints demonstrating that TCZ 162 mg SC QW and Q2W in combination with a 26 wk or 52 wk resp. prednisone tapering regime are effective at maintaining steroid-free remission in patients with GCA.

2.5. Clinical safety

Introduction

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. TCZ is available in 2 different pharmaceutical forms to allow either administration by intravenous (IV) infusion or by subcutaneous (SC) injection.

In adult patient both pharmaceutical forms of TCZ are approved. TCZ is indicated in combination with methotrexate (MTX), for the treatment of moderate to severe active rheumatoid arthritis (RA) in patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, TCZ can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

The recommended dose for IV administration is 8 mg/kg TCZ every 4 weeks (q4w).

For SC administration, the recommended dose is 162 mg once every week (qw).

Regarding the safety profile of TCZ in the adult RA population, unfavourable effects include infection, gastro-intestinal disorders, infusion reactions, skin disorders, neutropenia, elevation in hepatic enzymes and lipid parameters.

The safety data base supporting this application is derived primarily from the single pivotal Phase III Study WA28119. After the 52-week double-blind treatment period (reported in this assessment report), all patients entered the 104-week LTE/long-term follow-up (Part 2) of the study. Based on the investigator's assessment of GCA disease activity at the end of the 52-week double-blind period, the patient was either given the option to receive open-label TCZ 162 mg QW (in case of persistent disease activity/flare) or was followed up off treatment for maintenance of established remission at the investigators discretion. A patient's GCA therapy could be adjusted at any time during Part 2 of the study at the investigator's discretion and on the basis of disease activity. This could have included initiation/termination of open-label TCZ 162 mg QW and/or changes to corticosteroid or methotrexate (MTX) treatment.

In addition to the Phase III study, the following data are submitted as supportive safety data

- Results from a Phase II investigator-initiated trial (ML25676), studying intravenous (IV) TCZ in patients with newly diagnosed or relapsing GCA

Table 16 - Summary of studies contributing to safety evaluation in GCA

Study No. (Phase)	Study Design	Population	No. of Patients	Dose, Route, and Regimen
Pivotal Phase III Study				
WA28119 (Phase III)	Multi-center, randomized, double-blind placebo-controlled superiority study to assess the efficacy and safety of TCZ in patients with giant cell arteritis Part 1: 52-week blinded period for primary analysis Part 2: 104-week open-label extension.	Patients ≥ 50 years with new-onset GCA and with relapsing GCA	251[a] (149 receiving TCZ)	162 mg SC TCZ (QW) + 26-week prednisone taper regimen 162 mg SC TCZ (Q2W) + 26-week prednisone taper regimen SC placebo + 26-week prednisone taper regimen SC placebo + 52-week prednisone taper regimen
Supporting Study				
ML25676 (Phase II)	Single-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of TCZ + GC treatment compared with placebo + GC treatment in the induction and maintenance of disease remission in patients with newly diagnosed or relapsing giant cell arteritis	Patients ≥ 50 years with new-onset GCA and with relapsing GCA satisfying 1990 ACR criteria	30	8 mg/kg IV TCZ (13 infusions given in 4 week intervals until Week 52) + oral prednisolone (starting at 1 mg/kg per day) taper regimen IV placebo (13 infusions given in 4 week intervals until Week 52) + oral prednisolone (starting at 1 mg/kg per day) taper regimen

ACR: American College of Rheumatology; GC: glucocorticoids; GCA: Giant Cell Arteritis; IV: intravenous; QW: weekly; Q2W: every other week; SC: subcutaneous; TCZ: tocilizumab

[a] Of the 251 randomized patients, 1 patient who was randomized to the TCZ Q2W group withdrew the same day they were randomized, and did not receive any study treatment. This patient was excluded from the Safety analysis population.

Further the following data are also included in the submission

- Pooled long-term safety data with IV TCZ in the rheumatoid arthritis (RA) population, referred to as LTE All-exposure RA population
- Background rates of adverse events of special interest (AESIs) and glucocorticoid- induced toxicity information from an epidemiological analysis of the MarketScan health claims database

The MarketScan analysis is a retrospective cohort study of glucocorticoid use and AEs in patients with GCA (who were not treated with TCZ) in the United States from 1 January 2000 to 30 June 2015.

Background AESI rates and glucocorticoid induced toxicity in GCA (in absence of TCZ exposure) from the MarketScan analysis are presented to contextualize rates reported with TCZ treatment in Study WA28119.

Analysis of adverse events (AEs) reported in single case reports of patients with GCA treated with IV TCZ outside of clinical trials

Patient exposure

Study WA28119

The Safety population included data from 250 patients who received at least one administration of study drug and had at least one post-dose safety assessment (withdrawal, AE, death, laboratory assessment, or vital sign assessment). Of the 251 randomized patients, 1 patient who was randomized to the TCZ Q2W group withdrew prior to receiving their first dose of TCZ. This patient was excluded from the Safety analysis population.

Median study duration was identical (1.0 year) in all treatment groups. Based on the number of doses of SC study treatment (TCZ/ placebo) received, the patient-years of exposure were similar in the TCZ Q2W and placebo groups. Given that twice as many patients were randomized to the TCZ QW group, the total number of patient years of exposure (86.41 patient-years) was much higher than in the TCZ Q2W group (43.7 patient-years), PBO + 26 wk group (44.3 patient-years) and PBO + 52 wk group (46.0 patient-years).

Table 17 - Exposure to blinded SC study treatment (safety population)

Study Treatment Exposure - SC Double-blind study drug, Safety Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Treatment Duration (D)				
n	50	51	100	49
Mean (SD)	324.0 (79.4)	331.6 (83.4)	317.2 (96.7)	324.3 (82.0)
Median	358.0	358.0	358.0	358.0
Min - Max	44 - 368	43 - 369	9 - 365	6 - 371
Treatment Duration Category (D)				
n	50	51	100	49
0 - 91	3 (6.0%)	4 (7.8%)	8 (8.0%)	1 (2.0%)
92 - 183	1 (2.0%)	0	5 (5.0%)	5 (10.2%)
184 - 274	4 (8.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
275 - 365	41 (82.0%)	43 (84.3%)	84 (84.0%)	38 (77.6%)
>365	1 (2.0%)	3 (5.9%)	0	3 (6.1%)
Dose Intensity (%)				
n	50	51	100	49
Mean (SD)	98.5 (3.4)	98.0 (3.3)	97.9 (4.0)	98.7 (2.7)
Median	100.0	100.0	100.0	100.0
Min - Max	85 - 100	86 - 100	77 - 100	88 - 100
Number of doses				
n	50	51	100	49
Mean (SD)	46.3 (11.1)	47.1 (11.7)	45.1 (13.7)	46.5 (11.6)
Median	52.0	51.0	51.5	52.0
Min - Max	7 - 53	7 - 53	2 - 53	2 - 53
Total cumulative dose (mg)				
n	50	51	100	49
Mean (SD)	0.0 (0.0)	0.0 (0.0)	7304.6 (2215.4)	3785.5 (941.0)
Median	0.0	0.0	8343.0	4212.0
Min - Max	0 - 0	0 - 0	324 - 8586	162 - 4374
Missed Doses				
n	50	51	100	49
No missed dose	37 (74.0%)	29 (56.9%)	58 (58.0%)	36 (73.5%)
One missed dose	6 (12.0%)	12 (23.5%)	24 (24.0%)	5 (10.2%)
Two missed doses	1 (2.0%)	0	6 (6.0%)	4 (8.2%)
Three missed doses	1 (2.0%)	4 (7.8%)	3 (3.0%)	2 (4.1%)
Four missed doses	3 (6.0%)	4 (7.8%)	4 (4.0%)	1 (2.0%)
At least five missed doses	2 (4.0%)	2 (3.9%)	5 (5.0%)	1 (2.0%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the number of doses actually received divided by the expected number of doses multiplied by 100.
Program: /opt/BIOSTAT/prod/cnl1935e/i28119a/t_ex_sd.sas / Output: /opt/BIOSTAT/prod/cnl1935e/i28119a/reports/t_ex_sd_SE.out
11JUL2016 21:40 (PDRD) Page 1 of 1

Glucocorticoid-induced toxicity

Events that are consistent with glucocorticoid-induced toxicity from Part 1 of Study WA28119 were analysed retrospectively using criteria that were developed by the Sponsor prior to database lock.

Total prednisone exposure

Median total prednisone treatment duration was 52 weeks (1 year) in all treatment groups, accounting for open-label prednisone taper, blinded prednisone/placebo as well as escape and commercial prednisone (for concomitant conditions). Median total cumulative prednisone dose was identical in the TCZ QW and TCZ

Q2W groups (1862 mg). However, as a result of the increased use of escape glucocorticoid therapy (and longer prednisone taper period in the PBO + 52 wk group), median total cumulative prednisone dose was higher in the PBO + 26 wk (3296 mg) and PBO + 52 wk (3817.5 mg) groups.

Study WA28119 Part 2 – open-label extension (Part 2)

Eighty-eight patients included in the data analysis of Part 2 had at least 100 weeks of follow-up in the study. As of the data cut-off date (11 April 2016), some patients had continued in Part 2 of the study up to Week 136 (scheduled visit); hence the range for duration of follow-up in Part 2 ranges from 48 to 84 weeks. The majority (66/88) of these patients had received TCZ either during Part 1 or Part 2 of the study. Of the 88 patients; 50 had received either TCZ QW or TCZ Q2W during Part 1, and 27 of these patients started open-label TCZ during Part 2 of the study. Of the 38 patients, who were randomized to the placebo groups during Part 1, a further 16 patients received open-label TCZ during Part 2 of the study.

Exposure in PY is not summarized for this period because there was no predefined treatment regimen, leading to inconsistent exposure to study drug within or between patients.

Phase II investigator-initiated trial ML25676

Twenty patients received TCZ + prednisolone (hereafter referred to as the TCZ group) and 10 patients received placebo + prednisolone (hereafter referred to as the placebo group).

Clinical trial information from patients with RA treated with IV tocilizumab

The safety dataset (May 2012 data cut; referred to as the LTE all-exposure RA population) includes data from 4171 patients who received at least 1 dose of TCZ in the clinical trial program.

Adverse events

Study WA28119 (52 weeks double blind treatment)

Table 18 - Overview of adverse events

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Total number of patients with at least one AE	48 (96.0%)	47 (92.2%)	98 (98.0%)	47 (95.9%)
Total number of events	470	486	810	432
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	2 (4.0%)	0	6 (6.0%)	3 (6.1%)
Total number of patients with at least one				
AE with fatal outcome	0	0	0	0
Serious AE	11 (22.0%)	13 (25.5%)	15 (15.0%)	7 (14.3%)
Serious AE related to TCZ	4 (8.0%)	6 (11.8%)	4 (4.0%)	2 (4.1%)
Serious AE related to Prednisone	5 (10.0%)	4 (7.8%)	3 (3.0%)	1 (2.0%)
AE leading to withdrawal from blinded TCZ/Placebo	3 (6.0%)	0	11 (11.0%)	5 (10.2%)
AE leading to dose modification/interruption of blinded TCZ/Placebo	10 (20.0%)	11 (21.6%)	28 (28.0%)	8 (16.3%)
AE related to TCZ	21 (42.0%)	18 (35.3%)	52 (52.0%)	26 (53.1%)
AE related to Prednisone	31 (62.0%)	25 (49.0%)	50 (50.0%)	30 (61.2%)
Adverse Events of Special Interest:				
Infections and Infestations	38 (76.0%)	33 (64.7%)	75 (75.0%)	36 (73.5%)
Serious Infections	2 (4.0%)	6 (11.8%)	7 (7.0%)	2 (4.1%)
Opportunistic Infections	0	2 (3.9%)	0	1 (2.0%)
Malignancy AEs	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Malignancy AEs (excluding NMSC)	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Serious Hepatic AEs	0	0	0	0
Serious Stroke	0	1 (2.0%)	0	1 (2.0%)
Serious Myocardial Infarction	0	0	0	0
Anaphylactic Reaction AEs (SMQN)	0	0	0	0
Anaphylactic Reaction AEs (Sampson's criteria)	0	0	0	1 (2.0%)
Serious Gastrointestinal Perforation Adverse Events	0	0	0	0
Gastrointestinal Perforation AE Confirmed by Medical Review	0	0	0	0
Serious Bleeding AEs	0	0	0	0
Serious Demyelinating AEs	0	0	0	0

Investigator text for AEs encoded using MedDRA version 19.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Sources: ae_oview_SE, t_ae_SE_SER_INF

The numbers of individual events were numerically or proportionally (for comparison to TCZ QW) lower in the TCZ treatment groups (470 and 486 in the placebo groups vs. 810 events in the TCZ QW group [which included twice as many patients than the other groups] and 432 events in the TCZ Q2W group). This translates into numerically higher rates of AEs in the placebo groups compared with the TCZ groups:

PBO + 26 wk group 990.8 [95% CI: 903.2, 1084.5] AEs per 100 PY

PBO + 52 wk group 1011.2 [95% CI: 923.3, 1105.3] AEs per 100 PY vs.

TCZ QW 872.0 [95% CI: 813.0, 934.2] AEs per 100 PY

TCZ Q2W group 948.0 [95% CI: 860.7, 1041.7] AEs per 100 PY

Table 19 - Summary of adverse events by system organ class (Safety Population)

Summary of Adverse Events by SOC, Safety Population
Protocol: WA28119

MedDRA System Organ Class	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Total number of patients with at least one adverse event	48 (96.0%)	47 (92.2%)	98 (98.0%)	47 (95.9%)
Total number of events	470	486	810	432
INFECTIONS AND INFESTATIONS	38 (76.0%)	33 (64.7%)	75 (75.0%)	36 (73.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	34 (68.0%)	32 (62.7%)	63 (63.0%)	28 (57.1%)
NERVOUS SYSTEM DISORDERS	23 (46.0%)	22 (43.1%)	43 (43.0%)	22 (44.9%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	21 (42.0%)	14 (27.5%)	37 (37.0%)	25 (51.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	17 (34.0%)	17 (33.3%)	33 (33.0%)	25 (51.0%)
GASTROINTESTINAL DISORDERS	19 (38.0%)	15 (29.4%)	36 (36.0%)	18 (36.7%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	16 (32.0%)	17 (33.3%)	22 (22.0%)	11 (22.4%)
EYE DISORDERS	15 (30.0%)	14 (27.5%)	18 (18.0%)	13 (26.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	10 (20.0%)	14 (27.5%)	26 (26.0%)	10 (20.4%)
VASCULAR DISORDERS	13 (26.0%)	9 (17.6%)	23 (23.0%)	13 (26.5%)
INVESTIGATIONS	9 (18.0%)	8 (15.7%)	23 (23.0%)	7 (14.3%)
PSYCHIATRIC DISORDERS	13 (26.0%)	8 (15.7%)	12 (12.0%)	8 (16.3%)
METABOLISM AND NUTRITION DISORDERS	4 (8.0%)	7 (13.7%)	10 (10.0%)	7 (14.3%)
CARDIAC DISORDERS	6 (12.0%)	6 (11.8%)	8 (8.0%)	3 (6.1%)
EAR AND LABYRINTH DISORDERS	6 (12.0%)	6 (11.8%)	7 (7.0%)	4 (8.2%)
RENAL AND URINARY DISORDERS	4 (8.0%)	6 (11.8%)	7 (7.0%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (8.0%)	1 (2.0%)	8 (8.0%)	1 (2.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3 (6.0%)	3 (5.9%)	2 (2.0%)	3 (6.1%)
IMMUNE SYSTEM DISORDERS	3 (6.0%)	2 (3.9%)	2 (2.0%)	3 (6.1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	2 (3.9%)	5 (5.0%)	3 (6.1%)
ENDOCRINE DISORDERS	1 (2.0%)	2 (3.9%)	6 (6.0%)	0
SURGICAL AND MEDICAL PROCEDURES	3 (6.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
PRODUCT ISSUES	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
Percentages are based on N in the column headings.

Program: /opt/BIOSTAT/prod/cnl1935e/i28119a/t_ae.sas / Output: /opt/BIOSTAT/prod/cnl1935e/i28119a/reports/t_ae_SE_SUM.out
12JUL2016 0:11 Page 1 of 1

By preferred term, the most commonly reported all-grade AEs were headache (non- GCA related) reported in 27% of patients in the TCZ QW group, 20% of patients in the TCZ Q2W group, 32% of patients in the PBO + 26 wk group and 24% of patients in the PBO + 52 wk group, nasopharyngitis reported in 29% of patients in the TCZ QW group, 25% of patients in the TCZ Q2W group, 18% of patients in the PBO + 26 wk group and 26% of patients in the PBO + 52 wk group, edema peripheral reported in 16% of patients in the TCZ QW group, 25% of patients in the TCZ Q2W group, 16% of patients in the PBO + 26 wk group and 12% of patients in the PBO + 52 wk group, and arthralgia reported in 13% of patients in the TCZ QW group, 16% of patients in the TCZ Q2W group, 22% of patients in the PBO + 26 wk group and 16% of patients in the PBO + 52 wk group.

AEs considered related to blinded study treatment (TCZ, prednisone or both) by the investigator (i.e., TCZ, prednisone, or both) were reported in 68% of patients in the TCZ QW group, 74% of patients in the TCZ Q2W group, 64% of patients in the PBO + 26 wk group and 53% of patients in the PBO + 52 wk group. The SOCs with the highest incidence of AEs considered related to study treatment by the investigator were Infections and Infestations (most commonly [i.e., ≥ 5% overall incidence] nasopharyngitis, upper respiratory tract infection, bronchitis, cystitis, and oral herpes), Skin and Subcutaneous Tissue Disorders (most commonly alopecia), General Disorders and Administration Site Conditions (most commonly oedema peripheral), and Gastrointestinal Disorders.

Study WA28119 Part 2 – open-label extension

Eighty-eight patients were included in the Part 2 data cut. The majority (66/88) of these patients had received TCZ either during Part 1 or Part 2 of the study.

Eighty-one of the 88 patients (92.0%) reported at least one AE in Part 2 of Study WA28119. Causality has not been assessed in the evaluation of non-serious events.

The highest incidence of AEs was reported in the Infections and Infestations SOC (51/88 [58.0%]); most commonly nasopharyngitis (15/88 [17.0%]) and bronchitis (10/88 [11.4%]). This was followed by AEs in the Musculoskeletal and Connective Tissue Disorders SOC (44/88 [50.0%]; most commonly arthralgia (11/88 [12.5%]) and pain in extremity (6/88 [6.8%]), Nervous System Disorders SOC (23/88 [26.1%]); most commonly headache (7/88 [8.0%]), and General Disorders and Administration Site Conditions SOC

(19/88 [21.6%]); most commonly fatigue (5/88 [5.7%]).

Of the 404 AEs reported in Part 2 of Study WA28119, the majority were either mild (Grade 1; 282 events) or moderate (Grade 2; 92 events) in intensity. Twenty-eight severe (Grade 3) events were reported; the majority of which were from the SOCs of Infections and Infestations and Vascular Disorders.

Phase II investigator-initiated trial ML25676

Table 20 - Summary of adverse events (IV TCZ)

Adverse Events	Placebo + GC (N = 10)	TCZ + GC (N = 20)
Number of Patients with at least one adverse event	7 patients	15 patients
Total number of adverse events	23	26
Cardiovascular disease	5[a]	1
Gastrointestinal disease	1	4
Osteoporotic fracture	3	1
Musculoskeletal disease	8	5
GC-related hyperglycaemia and myopathia	3	3
Infectious disease	1	10
Skin disease	2	1
Cystic lesion mammary	0	1

GC = glucocorticoid; TCZ = tocilizumab.

[a] 1 cardiovascular-related death.

Source: Villiger et al. 2016

Clinical trial information from patients with RA treated with IV tocilizumab

Table 21 - Rates of adverse events per 100 patient years by 6-monthly periods to 1 year (Study WA28119 (Part 1) and LTE Rheumatoid Arthritis dataset

	GCA (Study WA28119)				RA
	PBO QW + 26 Weeks Prednisone Taper N = 50	PBO QW + 52 Weeks Prednisone Taper N = 51	TCZ QW + 26 Weeks Prednisone Taper N = 100	TCZ Q2W + 26 Weeks Prednisone Taper N = 49	IV TCZ LTE All Exposure N = 4171
Overall					
Duration in Study (PY)	47.44	48.06	92.89	45.57	16204.77
Patients [a] (Number of Events)	48 (470)	47 (486)	98 (810)	47 (432)	3941 (47970)
Rate per 100 Patient-Years	990.8	1011.2	872.0	948.0	296.0
95% CI	903.2, 1084.5	923.3, 1105.3	813.0, 934.2	860.7, 1041.7	293.4, 298.7
Months 0-6					
Duration in Study (PY)	22.66	22.82	44.85	22.35	1876.78
Patients [a] (Number of Events)	48 (293)	46 (268)	90 (493)	46 (253)	3003 (9021)
Rate per 100 Patient-Years	1292.8	1174.3	1099.2	1131.9	480.7
95% CI	1149.0, 1449.6	1037.9, 1323.6	1004.3, 1200.6	996.7, 1280.3	470.8, 490.7
Months 7-12					
Duration in Study (PY)	21.16	21.54	41.09	19.98	1679.07
Patients [a] (Number of Events)	38 (157)	36 (185)	79 (271)	38 (158)	2405 (6100)
Rate per 100 Patient-Years	742.0	858.7	659.5	790.8	363.3
95% CI	630.5, 867.6	739.4, 991.8	583.3, 742.9	672.3, 924.1	354.2, 372.5

GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

[a] Patients with at least one event.

Source: WA28119 t_ae_rate_SE.out , RA LTE STae_rategp6_all.

Overall, the safety profile observed with SC TCZ in GCA in Study WA28119 (Part 1) is generally consistent with the established safety profile of IV TCZ in RA, with the highest rates reported in the Infections and Infestations SOC in both populations (data not shown).

Serious adverse event / deaths / other significant events

Study WA28119 (52 weeks double blind treatment)

Table 22 - Rates of SAEs per 100 patient years by 6 monthly periods up to 1 year Study WA28119 (Part 1) and LTE RA Dataset

	GCA (Study WA28119)				RA
	PBO QW+ 26 Weeks Prednisone Taper N = 50	PBO QW+ 52 Weeks Prednisone Taper N = 51	TCZ QW+ 26 Weeks Prednisone Taper N = 100	TCZ Q2W+ 26 Weeks Prednisone Taper N = 49	IV TCZ LTE All Exposure N = 4171
Overall					
Duration in Study (PY)	47.44	48.06	92.89	45.57	16204.77
Patients* (Number of Events)	11 (15)	13 (21)	15 (27)	7 (10)	1325 (2338)
Rate per 100 Patient-Years	31.6	43.7	29.1	21.9	14.4
95% CI	17.7, 52.2	27.0, 66.8	19.2, 42.3	10.5, 40.4	13.9, 15.0
Months 0-6					
Duration in Study (PY)	22.66	22.82	44.85	22.35	1876.78
Patients* (Number of Events)	8 (10)	8 (13)	10 (16)	3 (3)	263 (313)
Rate per 100 Patient-Years	44.1	57.0	35.7	13.4	16.7
95% CI	21.2, 81.1	30.3, 97.4	20.4, 57.9	2.8, 39.2	14.9,18.6
Months 7-12					
Duration in Study (PY)	21.16	21.54	41.09	19.98	1679.07
Patients* (Number of Events)	3 (5)	7 (8)	6 (10)	4 (6)	221 (268)
Rate per 100 Patient-Years	23.6	37.1	24.3	30.0	16.0
95% CI	7.7, 55.1	16.0, 73.2	11.7, 44.8	11.0, 65.4	14.1, 18.0

GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.
* Patients with at least one event

Table 23 - Summary of common SAEs by System by SOC 100 patient years in the TCZ treatment groups in Study WA28119 (part 1)

Serious Adverse Events System Organ Class	TCZ QW+ 26 Weeks Prednisone Taper N = 100 92.89 PY	TCZ Q2W+ 26 Weeks Prednisone Taper N = 49 45.57 PY
	Patients (Number of Events) Rate per 100 PY 95% CI	
Infections and Infestations	7 (9) 9.7 4.4, 18.4	2 (2) 4.4 0.5, 15.9
Vascular Disorders	4 (5) 5.4 1.7, 12.6	2 (2) 4.4 0.5, 15.9
Injury, Poisoning and Procedural Complications	3 (3) 3.2 0.7, 9.4	1 (1) 2.2 0.1, 12.2
Cardiac Disorders	2 (2) 2.2 0.3, 7.8	0 0.0 0.0, 8.1
Respiratory, Thoracic and Mediastinal Disorders	2 (2) 2.2 0.3, 7.8	1 (1) 2.2 0.1, 12.2

PY = patient years; QW = weekly; Q2W = every other week; TCZ = tocilizumab.
Source: WA28119: t_ae_rate_ah105_SE_SER.

The SAE rate per 100 PY of exposure was numerically lower in both TCZ arms compared with the placebo arms, with the highest AE rate occurring in the PBO + 52 wk group.

The most frequently reported SAEs occurred in the SOC of Infections and Infestations, with events for 7% (7/100) of patients in the TCZ QW group, 4% (2/49) of patients in the TCZ Q2W group, 4% (2/50) of patients in the PBO + 26 wk group, and 12% (6/51) of patients in the PBO + 52 wk group. By preferred term, the only SAEs reported in more than 1 patient in any treatment group were gastroenteritis and herpes zoster, both reported by 2 patients in the PBO + 52 wk group (and 1 patient in the TCZ QW group), and

hypertensive crisis reported by 2 patients in the TCZ QW group

No deaths were reported during Part 1 of Study WA28119.

Study WA28119 Part 2 – open-label extension

One patient in the PBO + 26 wk group (Part 1) reported a life-threatening (Grade 4) SAE of urosepsis in Part 2.

One fatal event of aortic dissection was reported in Part 2 of Study WA28119 until the cut-off date of 11 April 2016.

Phase II investigator-initiated trial ML25676

Seven SAEs were reported in 7 patients (35%) in the TCZ group compared with10 events in 5 patients (50%) in the placebo group.

Clinical trial information from patients with RA treated with IV tocilizumab

In the LTE All-exposure RA population, 94/4171 patients died, leading to an overall rate of 0.6 events per 100 PY. The most common causes of death by SOC were infections (25 patients), cardiac disorders (16 patients), and malignancies.

Table 24 - Summary of serious adverse events

SAEs	Placebo + GC (N = 10)	TCZ + GC (N = 20)
Number of Patients with at least one SAE	5 patients	7 patients
Total number of SAEs	10	7
Cardiovascular	3	1
Gastrointestinal	1	3
Osteoporotic fracture	2	0
Back pain	2	0
GC-related hyperglycaemia and myopathia	2	1
Infectious disease	0	1
Skin disease	0	1

GC = glucocorticoid; SAE = serious adverse event; TCZ = tocilizumab.
Source: Villiger et al. 2016.

One patient in the TCZ group had severe headache with tinnitus leading to admittance to hospital, the symptoms were not judged to be caused by GCA.

Three serious gastrointestinal complications were reported in the TCZ group: one patient not taking prescribed pantoprazole developed a pre-pyloric ulcer perforation, the second suffered hepatopathy due to an undefined viral infection, and the third patient underwent gastrointestinal endoscopy due to gastrointestinal bleeding 12 days after start of TCZ treatment.

One eye infection due to Moraxella catarrhalis and herpes led to inpatient treatment in a patient in the TCZ group.

A case of Stevens-Johnson syndrome developed in another TCZ patient 3 days after the third infusion, the causal relationship could not be determined because multiple drugs had been started within the possible timeframe.

The causality of AEs reported above in the TCZ and placebo treatment groups was not provided in the publication of the study.

Glucocorticoid-related comorbidities included severe psychosis in one of the patients in the TCZ group and

immobilizing steroid-induced myopathy and hyperglycaemia in two patients in the placebo group.

One cardiovascular-related death was reported in the placebo group.

Table 25 - Summary of common SAs by SOC per 100 patient years LTE RA dataset

Serious Adverse Events System Organ Class	IV TCZ LTE All Exposure N = 4171 16204.77 PY
	Patients (Number of Events) Rate per 100 PY 95% CI
Infections and Infestations	531 (717) 4.4 4.1, 4.8
Injury, Poisoning and Procedural Complications	192 (202) 1.3 1.1, 1.4
Neoplasms Benign, Malignant and Unspecified	173 (186) 1.2 1.0, 1.3
Gastrointestinal Disorders	161 (186) 1.2 1.0, 1.3
Cardiac Disorders	130 (172) 1.1 0.9, 1.2

IV = intravenous; LTE = long-term extension; PY = patient years; TCZ = tocilizumab.
Source: LTE RA: STae_rategp6_s.

Adverse events of special interest

Infections (Infections and Infestations System Organ Class [SOC])

- Study WA28119 (52 weeks double blind treatment)

There were no marked differences in the overall incidence of patients with infections between the TCZ QW (75%), TCZ Q2W (74%), PBO + 26 wk (76%), and PBO + 52 wk (65%) treatment groups.

The rates of infections were comparable between the TCZ and placebo groups in Study WA28119. Overall, the rates of infections were higher in Study WA28119 (Part 1) compared with the LTE All-exposure RA population.

Table 26 - Rates of infections per 100 Patient-years overall and by 6-monthly periods up to 1 year, Study WA28119 (Part 1) and LTE RA dataset

	GCA				RA LTE
AESI	PBO QW + 26 Week Prednisone Taper n = 50 47.44 PY	PBO QW + 52 Week Prednisone Taper n = 51 48.06 PY	TCZ QW + 26 Week Prednisone Taper n = 100 92.89 PY	TCZ Q2W + 26 Week Prednisone Taper n = 49 45.57 PY	IV TCZ All Exposure n = 4171 16204.77 PY
	Patients (Number of Events) Rate per 100 PY 95% CI				
Infections (Overall)	38 (74) 156.0 122.5, 195.8	33 (101) 210.2 171.2, 255.4	75 (186) 200.2 172.5, 231.2	36 (73) 160.2 125.6, 201.4	3183 (15026) 92.7 91.25, 94.2
Months 0-6	25 (39) 172.1 122.4, 235.2	25 (51) 223.5 166.4, 293.8	57 (107) 238.6 195.5, 288.3	27 (39) 174.5 124.1, 238.5	1488 (2215) 118.0 113.2, 123.0
Months 7-12	21 (28) 132.3 87.9, 191.3	21 (42) 194.9 140.5, 263.5	41 (67) 163.1 126.4, 207.1	19 (30) 150.1 101.3, 214.3	1248 (1776) 105.8 100.9, 110.8

AESI = adverse events of special interest; GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Notes: MedDRA version 19.0 was used for coding AEs in Study WA28119 and MedDRA version 15.0 was used for coding AEs in the IV TCZ All Exposure Population.

Rates for non-serious infections are not easily captured or validated as part of health insurance claims data in the MarketScan database; hence not reported.

Source: WA28119: t_ae_SE_inf, t_ae_rate_SE; LTE RA: STae_rategp6_inf.

The most common types of infections across all treatment groups were nasopharyngitis, upper respiratory tract infection, bronchitis, and urinary tract infection. Dose interruption because of infections occurred in 18% of patients in the TCZ QW group, 14% of patients in the TCZ Q2W group, 14% of patients in the PBO + 26 wk group, and 20% of patients in the PBO + 52 wk group.

Serious infections (including opportunistic infections)

Serious infections were reported in 7% (7/100) of patients in the TCZ QW group, 4% (2/49) of patients in the TCZ Q2W group, 4% (2/50) of patients in the PBO + 26 wk group, and 12% (6/51) of patients in the PBO + 52 wk group. This was reflected in the rates of serious infections (including opportunistic infections) in the TCZ groups that were also numerically lower compared with the placebo groups but with overlapping CIs.

The rates of opportunistic infections were comparable between the TCZ and placebo groups

Table 27 - Overview of serious infections and opportunistic infections per 100 patient-years in Study WA28119 (Part 1), LTE RA and Giant Cell Arteritis MarketScan dataset

MarketScan Database

	GCA				RA LTE	GCA
AESIs	PBO QW + 26 Week Prednisone Taper n = 50 47.44 PY	PBO QW + 52 Week Prednisone Taper n = 51 48.06 PY	TCZ QW + 26 Week Prednisone Taper n = 100 92.89 PY	TCZ Q2W + 26 Week Prednisone Taper n = 49 45.57 PY	IV TCZ All Exposure n = 4171 16204.77 PY	MarketScan n = 4804 4804.00 PY[a]
	Patients (Number of Events) Rate per 100 PY 95% CI					
Serious infections	2 (2) 4.2 0.5, 15.2	6 (6) 12.5 4.6, 27.2	7 (9) 9.7 4.4, 18.4	2 (2) 4.4 0.5, 15.9	531 (717) 4.4 4.1, 4.8	1113 28.9 27.2, 30.6
Opportunistic infections	0 0.00 0.0, 7.8	2 (2) 4.2 0.5, 15.0	0 0.0 0.0, 4.0	1 (2) 4.4 0.5, 15.9	35 (38) 0.2 0.2, 0.3	163 3.5 3.0, 4.1

AESI = adverse events of special interest; GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Notes: MedDRA version 19.0 was used for coding AEs in Study WA28119 and MedDRA version 15.0 was used for coding AEs in the IV TCZ All Exposure Population.

In MarketScan, individual events are counted only once in each patient over 52 weeks; therefore number of patients and number of events are same.

[a] Only serious opportunistic infections are included in the Marketscan data because non-serious opportunitistic infections are not easily captured of validated as part of health insurance claims data in the MarketScan database.

Source: WA28119: t_ae_SE_SER_INF, t_ae_SE_OPP, LTE RA: STae_rategp6_s_inf, STae_rategp6_opp, Real World Evidence report.

The serious infection events of gastroenteritis and herpes zoster were both observed in 2 patients each in the PBO + 52 wk group. All other serious infections were single occurrences. Three urinary tract-related serious events (urinary tract infection, urosepsis, and pyelonephritis) were reported in a single patient.

Opportunistic infections were reported in 2 patients in the PBO + 52 wk group (Grade 3 genital herpes zoster and Grade 1 cytomegalovirus infection) and 1 patient in the TCZ Q2W group (Grade 1 oropharyngeal candidiasis)

In addition to the opportunistic infections defined by the Roche AEGT basket, the sponsor performed a manual review of additional potential opportunistic infections reported in the Infections and Infestations SOC ('herpes zoster' and 'tuberculosis'). Herpes zoster was reported in 5 patients (5.0%) in the TCZ QW group, 2 patients (4.1%) in the TCZ Q2W group, 0 patients in the PBO + 26 wk group and 2 patients (3.9%) in the PBO + 52 wk group. Most of these events were non-serious, Grade 2 events, which did not result in a change to study treatment.

There were no reports of tuberculosis in study WA28119.

Hypersensitivity

Table 28 - Overview of hypersensitivity per 100 patient-years in Study WA28119 (Part 1) and LTE RA dataset

	GCA				RA LTE
AESIs	PBO QW + 26 Week Prednisone Taper n = 50 47.44 PY	PBO QW + 52 Week Prednisone Taper n = 51 48.06 PY	TCZ QW + 26 Week Prednisone Taper n = 100 92.89 PY	TCZ Q2W + 26 Week Prednisone Taper n = 49 45.57 PY	IV TCZ All Exposure n = 4171 16204.77 PY
	Patients (Number of Events) Rate per 100 PY 95% CI				
Hypersensitivity	6 (11) 23.2 11.6, 41.5	3 (8) 16.5 7.2, 32.8	11 (25) 26.9 17.4, 39.7	6 (8) 17.6 7.6, 34.6	992 (1686)[a] 10.4 9.9, 10.9

AESI = adverse events of special interest; GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Notes: MedDRA version 19.0 was used for coding AEs in Study WA28119 and MedDRA version 15.0 was used for coding AEs in the IV TCZ All Exposure Population.

Hypersensitivity reactions are not easily captured or validated in health insurance claims data.

[a] For hypersensitivity events, output only contains adverse events which are defined as occurring during or within 24 hours of an infusion/injection of study medication, and not deemed "unrelated" to trial treatment.

Source: WA28119: l_ae_hyp_ah105_SE, LTE RA: STae_rategp8_rel24, Real World Evidence report.

The rates of potential hypersensitivity reactions were comparable between the TCZ and placebo groups in Study WA28119 (see table 28). The rates of potential hypersensitivity reactions were higher in Study WA28119 (Part 1) compared with the LTE All-exposure RA population. However, the rates in Study WA28119 (Part 1) are based on only 52 events and low exposure, the 95% CI for the rates are wide and often overlapping between the two populations.

Injection site reactions

Table 29 - Overview of injection site reactions per 100 patient-years in Study WA28119 (Part 1) and LTE RA dataset

	GCA				RA	
	Study WA28119				Studies WA22762, NA25220	
	PBO QW + 26 Week Prednisone Taper	PBO QW + 52 Week Prednisone Taper	TCZ QW + 26 Week Prednisone Taper	TCZ Q2W + 26 Week Prednisone Taper	SC TCZ QW	SC TCZ Q2W
	n = 50	n = 51	n = 100	n = 49	n = 631	n = 437
AESIs	47.44 PY	48.06 PY	92.89 PY	45.57 PY	1013.26 PY	404.34 PY
	Patients (Number of Events) Rate per 100 PY 95% CI					
Injection Site Reactions	5 (5) 10.5 3.4, 24.6	1 (1) 2.1 0.1, 11.6	6 (7) 7.5 3.0, 15.5	7 (7) 15.4 6.2, 31.7	77 (264) 26.1 23.0, 29.4	39 (89) 22.0 17.7, 27.1

AESI = adverse events of special interest; GCA = giant cell arteritis; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; SC = subcutaneous; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Notes: MedDRA version 19.0 was used for coding AEs in Study WA28119, MedDRA version 16.1 was used for coding AEs in Study NA25220, and MedDRA version 14.1 was used for coding AEs in Study WA22762.

Injection-site reaction events that occur on the same day at the same site in a patient are counted once.

Injection-site reactions are not easily captured or validated in health insurance claims data; hence not reported for MarketScan.

Source: WA28119: l_ae_ah105_SE_ISR, NA25220: staerate01_isreact_2, slae05_isr WA22762: staerate01_isreact_2, slae05_isr.

Malignancies

Table 30 - Overview of malignancies per 100 patient-years in Study WA28119 (Part 1) LTE RA, and Giant Cell Arteritis MarketScan dataset

	GCA				RA LTE	GCA
	PBO QW + 26 Week Prednisone Taper	PBO QW + 52 Week Prednisone Taper	TCZ QW + 26 Week Prednisone Taper	TCZ Q2W + 26 Week Prednisone Taper	IV TCZ All Exposure	MarketScan
	n = 50	n = 51	n = 100	n = 49	n = 4171	n = 4804
AESIs	47.44 PY	48.06 PY	92.89 PY	45.57 PY	16204.77 PY	4804.00 PY
	Patients (Number of Events) Rate per 100 PY 95% CI					
Malignancies	1 (2) 4.2 0.5, 15.2	1 (1) 2.1 0.1, 11.6	1 (1) 1.1 0.0, 6.0	0 0.0 0.0, 8.1	221 (249) 1.5 1.4, 1.7	176 4.1 3.5, 4.7

AESI = adverse events of special interest; GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Notes: MedDRA version 19.0 was used for coding AEs in Study WA28119 and MedDRA version 15.0 was used for coding AEs in the IV TCZ All Exposure Population.

In MarketScan, individual events are counted only once in each patient over 52 weeks.

Source: WA28119: t_ae_SE_MALIG, LTE RA: STae_rategp6_mal, Real World Evidence report.

Stroke

Table 31 - Overview of stroke events per 100 patient-years in Study WA28119 (Part 1) and LTE RA dataset and Giant Cell Arteritis MarketScan database

	GCA				RA LTE	GCA
AESIs	PBO QW + 26 Week Prednisone Taper n = 50 47.44 PY	PBO QW + 52 Week Prednisone Taper n = 51 48.06 PY	TCZ QW + 26 Week Prednisone Taper n = 100 92.89 PY	TCZ Q2W + 26 Week Prednisone Taper n = 49 45.57 PY	IV TCZ All Exposure n = 4171 16204.77 PY	MarketScan n = 4804 4804.00 PY
	Patients (Number of Events) Rate per 100 PY 95% CI					
Stroke	0 0.0 0.0, 7.8	1 (1) 2.1 0.1, 11.6	0 0.0 0.0, 4.0	1 (1) 2.2 0.1, 12.2	51 (52) 0.3 0.2, 0.4	211 4.6 4.0, 5.3

AESI = adverse events of special interest; GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Notes: MedDRA version 19.0 was used for coding AEs in Study WA28119 and MedDRA version 15.0 was used for coding AEs in the IV TCZ All Exposure Population.

In MarketScan, individual events are counted only once in each patient over 52 weeks.

Both stroke events in Study WA28119 were classed as serious.

Source: WA28119: t_ae_SE_STRK, LTE RA: STae_rategp6_sstr_all, Real World Evidence report.

Anaphylaxis

No AEs as defined by the Anaphylactic Reaction SMQ Narrow, were reported. Two anaphylactic AEs (eye pruritus, dyspnea) were identified in a single patient in the TCZ Q2W group, using Sampson's criteria.

Serious bleeding, serious myocardial infarction, serious gastrointestinal perforation, serious hepatic events, serious demyelinating events

Table 32 - Overview of adverse events of special interest 100 patient-years in Study WA28119 (Part 1) and LTE RA dataset and Giant Cell Arteritis MarketScan database

	GCA				RA LTE	GCA
AESIs	PBO QW + 26 Week Prednisone Taper n = 50 47.44 PY	PBO QW + 52 Week Prednisone Taper n = 51 48.06 PY	TCZ QW + 26 Week Prednisone Taper n = 100 92.89 PY	TCZ Q2W + 26 Week Prednisone Taper n = 49 45.57 PY	IV TCZ All Exposure n = 4171 16204.77 PY	MarketScan n = 4804 4804.00 PY
	Patients (Number of Events) Rate per 100 PY 95% CI					
Serious bleeding events	0 0.0 0.0, 7.8	0 0.0 0.0, 7.7	0 0.0 0.0, 4.0	0 0.0 0.0, 8.1	62 (68) 0.4 0.3, 0.5	195 4.2 3.6, 4.8
Serious myocardial infarction	0 0.0 0.0, 7.8	0 0.0 0.0, 7.7	0 0.0 0.0, 4.0	0 0.0 0.0, 8.1	43 (44) 0.3 0.2, 0.4	113 2.4 2.0, 2.9
Serious GI perforations	0 0.0 0.0, 7.8	0 0.0 0.0, 7.7	0 0.0 0.0, 4.0	0 0.0 0.0, 8.1	31 (33) 0.2 0.1, 0.3	26 0.5 0.4, 0.8
Serious hepatic events	0 0.0 0.0, 7.8	0 0.0 0.0, 7.7	0 0.0 0.0, 4.0	0 0.0 0.0, 8.1	7(7) 0.0 0.0, 0.1	6 0.1 0.0, 0.3
Serious demyelinating events	0 0.0 0.0, 7.8	0 0.0 0.0, 7.7	0 0.0 0.0, 4.0	0 0.0 0.0, 8.1	3 (3) 0.0 0.0, 0.1	31 0.7 0.4, 0.9

AESI = adverse events of special interest; GCA = giant cell arteritis; GI = gastrointestinal; IV = intravenous; LTE = long-term extension; PBO = placebo PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Notes: MedDRA version 19.0 was used for coding AEs in Study WA28119 and MedDRA version 15.0 was used for coding AEs in the IV TCZ All Exposure Population.

In MarketScan, individual events are counted only once in each patient over 52 weeks.

Source: WA28119: t_ae_oview_SE, LTE RA: STae_rategp6_s_bleed, STae_rategp6_s_mi, STae_rategp6_gc, STae_rategp6_s_hep, STae_rategp6_s_dmyl, Real World Evidence report.

- Study WA28119 Part 2 – open-label extension

Table 33 - Overview of adverse events of special interest 100 patient-years in Study WA28119 (Part 2)

Treatment Group (Part 1)	Patient Number	Subtype	AESI	Onset Day	On OL TCZ at time of event (Yes/No)	TCZ Exposed (Yes/No)
PBO QW + 26 Weeks Prednisone Taper	264749/10501	Relapsing	Urosepsis	802	Yes	Yes
	253749/10381	Relapsing	Basal cell carcinoma	412	No	No
	253752/10562	Relapsing	Cerebrovascular accident	542	Yes	Yes
PBO QW + 52 Weeks Prednisone Taper	253747/10343	Relapsing	Troponin increased	697	Yes	Yes
TCZ QW + 26 Weeks Prednisone Taper	253755/10264	Relapsing	Gastroenteritis	589	No	Yes
	255228/10482	Relapsing	Basal cell carcinoma	780	No	Yes
	255511/10422	New Onset	Invasive ductal breast carcinoma	384	No	Yes
	255228/10484	Relapsing	Optic neuritis	379	No	Yes
TCZ Q2W + 26 Weeks Prednisone Taper	N/A	N/A	N/A	N/A	N/A	N/A

AESI = adverse event of special interest; N/A = not applicable; OL = open label; PBO = placebo; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Source: l_ae_p2_SE, l_ex_SE, l_ds_IT.

- Analysis of adverse events in single case reports of patients with GCA Treated with IV tocilizumab

outside of clinical trials

Of the 105 case reports reviewed none were published with a primary focus on safety of TCZ. No AEs were reported following treatment with IV TCZ for the majority of patients, and safety data were not provided for a few cases in these published reports. The nature of the events reported was consistent with the established safety profile of TCZ. Four deaths were reported due to myocardial infarction, septic shock, stroke, and sepsis (Toussirot et al. 2016).

Laboratory findings

Study WA28119 (52 weeks double blind treatment)

Decreases from baseline were observed in mean and median neutrophil and platelet counts.

Neutropenia (including “decreased neutrophil count”) was reported as an AE in 4 patients in the TCZ QW group and 2 patients in the TCZ Q2W group. One patient with neutropenia in the TCZ QW group was withdrawn from all study treatment because of the event. An additional 2 patients in the TCZ QW group, had a TCZ study treatment dose interruption/modification due to neutropenia. Review of the clinical listings showed that there was no association between Grade 3 or 4 events of neutropenia and serious infections.

Thrombocytopenia (including platelet count decreased) was reported as an AE in 2 patients in the TCZ Q2W group. Neither patient was withdrawn from study treatment because of the event. One patient (255731/11201) had a TCZ study treatment dose interruption/modification due to both platelet count decreased and ALT increased. Both events were Grade 1 in severity and resolved without sequelae.

Neither of the thrombocytopenia events was associated with a bleeding event.

Notable changes from baseline were observed for liver (ALT, AST) and lipid (total cholesterol, LDL cholesterol) parameters as well as glycated haemoglobin (Hb A1c). No clinically relevant changes over time were observed for other serum chemistry parameters.

“Alanine aminotransferase increased” was reported as an AE in 5 patients in the TCZ QW group, and 2 patients in each of the TCZ Q2W and PBO + 26 wk groups. “Aspartate aminotransferase increased” was reported as an AE in 4 patients in the TCZ QW group, and 1 patient in each of the TCZ Q2W and PBO + 26 wk groups. No patients were withdrawn from study treatment because of these AEs. However, TCZ study treatment dose interruptions/modifications due to these AEs were reported for 4 patients in the TCZ QW group, 1 patient in the TCZ Q2W group.

“Hepatic enzyme increased” was reported as an AE in 4 patients in the TCZ QW group and 2 patients in the PBO + 52 wk group. One event of “hepatic enzyme increased” in the PBO + 52 wk group was reported as a SAE (Grade 4) and led to TCZ study treatment interruption. None of the other events led to treatment withdrawal or study treatment interruption.

No AEs associated with other serum chemistry parameters (i.e., total bilirubin, alkaline phosphatase, and lipids) were reported in the study.

Phase II investigator-initiated trial ML25676

Table 34 - Laboratory values outside the normal range: Phase II investigator-initiated trial ML25676

	Placebo + GC (N = 10)		TCZ + GC (N = 20)	
	Baseline	Follow-up	Baseline	Follow-up
	No. of Episodes (Patients)			
Abnormal Transaminase Levels				
ALAT >70 U/l (women) or >100 U/l (men)	1 (1)	3 (2)	0	5 (2)
ASAT >70 U/l (women) or >100 U/l (men)	1 (1)	0	0	2 (2)
Hematology Abnormalities				
Leucopenia (leucocytes <3.5*10^9/L)	0	1 (1)	1 (1)	15 (6)
Neutropenia (neutrophiles <1.6*10^9/L)	0	0	0	9 (4)
Thrombocytopenia (thrombocytes <140*10^9/L)	0	4 (2)	0	15 (5)
Lipid Abnormalities				
Cholesterol >5.2 mmol/L	3 (3)	8 (5)	9 (9)	37 (18)
Triglycerides >1.7 mmol/L	0	7 (5)	2 (2)	20 (9)

GC = glucocorticoids; TCZ = tocilizumab.

Immunogenicity

The anti-drug antibody (ADA) assay applied in the TCZ development program is a quasi-quantitative assay, in which ADA levels were determined against a calibration curve generated from an anti-TCZ antibody positive control. The "relative ADA concentration" is provided in table 35 below for those GCA patients who developed ADA during the study.

Table 35 – Patients with treatment-induced ADA up to week 52 (safety population)

Patient ID	Treatment Group	Study Week that ADA was Positive	Confirmation Assay (ng_equivalents/mL)
253738/10842	PBO QW + 26 wk	Week 36	71.9
253751/10207	PBO QW + 52 wk	Week 52	72.3
255251/10221	TCZ QW	Week 24	31.6
255251/10227	TCZ Q2W	Week 24	48.6
263034/10628	TCZ Q2W	Week 24	38.1
255226/10862	TCZ Q2W	Week 36	182

Overall, the proportions of patients who developed treatment-induced ADA were low across treatment groups. No effects of ADA on safety, efficacy, or PK were observed

Safety in special populations

No safety analyses based on demographic and other intrinsic factors (age, gender, race, weight, BMI, medical history) were performed.

Safety related to drug-drug interactions and other interactions

There was no formal drug-drug interaction measurements carried out during GiACTA and ML25676 studies.

Potential indirect effect of TCZ on the expression of CYP3A4 metabolising enzyme and a consequent increased elimination of prednisone is discussed in the Clinical Pharmacology subsection of this AR.

Discontinuation due to adverse events

Table 36 - Rates of adverse events leading to TCZ withdrawal in the TCZ treatment groups in Study WA28119 (Part 1) and LTE RA dataset

GCA (Study WA28119)		RA LTE
TCZ QW + 26 Week Prednisone Taper n = 100 92.89 PY	TCZ Q2W + 26 Week Prednisone Taper n = 49 45.57 PY	IV TCZ All Exposure n = 4171 16204.77 PY
Patients (Number of Events) Rate per 100 PY 95% CI		
11 (22) 23.7 14.8, 35.9	5 (6) 13.2 4.8, 28.7	788 (793) 4.9 4.6, 5.3

GCA = giant cell arteritis; IV = intravenous; LTE = long-term extension; PY = patient years; RA = rheumatoid arthritis; QW = weekly; Q2W = every other week; TCZ = tocilizumab.
Source: WA28119: I_ae_SE_DSC; LTE RA: STae_rategp6_wd.

In Study WA28119 11 patients (11%) in the TCZ QW group, 5 patients (10%) in the TCZ Q2W group, 3 patients (6%) in the PBO + 26 wk group and no patient in the PBO + 52 wk group experienced ARs leading the withdrawal. No individual AE preferred term was reported by more than 1 patient in any treatment group

The most common AEs that resulted in withdrawal of study treatment in the LTE all-exposure RA population were associated with the Infections and Infestations.

Phase II investigator-initiated trial ML25676

Three patients were withdrawn from treatment prior to Week 12 due to AEs (1 patient, TCZ group) and SAEs (1 patient each in the TCZ and placebo groups).

Post marketing experience

TCZ is currently approved worldwide for the treatment of RA (IV and SC formulations), polyarticular juvenile idiopathic arthritis (IV formulation), and systemic juvenile idiopathic arthritis (IV formulation). In India and Japan, TCZ has an additional indication for treatment in Castleman's disease (IV formulation).

Since the IBD (11 April 2005) to 10 April 2016, an estimated cumulative total of 664,900 patients (522,482 PY) have received TCZ from marketing experience. The cumulative post-marketing exposure to SC TCZ is 92,216 patients (74,669 PY).

Cumulatively up to 10 April 2016, a total of 154,459 events had been recorded on the Company Global Safety Database. Of these, 42,797 events were considered as SAEs. The most common AEs (≥ 10%) from post-marketing sources were within the SOCs of Infections and Infestations (16.4%); General Disorders and Administration Site Conditions (15.7%), Musculoskeletal and Connective Tissue Disorders (11.7%), and Investigations (10%).

The safety profile of SC TCZ (with the exception of ISRs, which were more common with SC TCZ) was comparable with the safety profile of IV TCZ. No new or unexpected adverse drug reactions were observed with the SC formulation.

2.5.1. Discussion on clinical safety

The clinical safety data supporting this application are derived primarily from the pivotal study WA28119. Data from 250 patients treated for 52 weeks (Part 1) period and interim data from 88 patients in the LTE phase (Part 2) who had at least 100 weeks of follow up are included in the safety data base. The data base is further supported by results from a Phase II investigator-initiated trial (ML25676), studying intravenous (IV) TCZ in patients with newly diagnosed or relapsing GCA; pooled long-term safety data with IV TCZ in the rheumatoid arthritis (RA) population, which included 4171 patients, and analysis of adverse events (AEs) reported in single case reports of patients with GCA treated with IV TCZ outside of clinical trials. As reference background rates of adverse events of special interest (AESIs) and glucocorticoid- induced toxicity information from an epidemiological analysis of the MarketScan health claims database are included in the submission. Although the clinical trial database for GCA is small, given the long experience with TCZ IV and TCZ SC formulation, this is considered acceptable by CHMP.

In Part 1 of study WA28119 most patients in the study experienced at least one AE, with the proportion of such patients ranging between 92.2% and 98.0% across treatment groups. The number of individual events were numerically lower in the TCZ treatment groups (470 events in the PBO + 26 wk group and 486 in the PBO + 52 wk groups vs 432 events in the TCZ Q2W group and 810 events in TCZ QW [which included twice as many patients than the other groups]). This translates into numerically higher rates of 990.8 AEs [95% CI: 903.19, 1084.5] or 1011.2 [95% CI: 923.31, 1105.3] AEs per 100 patient years (PY) in the PBO + 26 wk and PBO + 52 wk groups, respectively, versus 872.0 AEs [95% CI: 813.00, 934.21] or 948.0 [95% CI: 860.67, 1041.7] AEs per 100 PY in the TCZ QW and Q2W groups, respectively.

The percentage of patients who experienced at least one AE during the 52 week double-blind study period was comparable between the different treatment groups. The SOC with the highest incidence of all-grade AE reporting was infections and infestations. The next highest incidence was in the Musculoskeletal and Connective Tissue Disorders SOC.

The SAE rate per 100 PY of exposure was numerically lower in both TCZ arms (29.1 [95% CI: 19.2, 42.3] events per 100 PY in the TCZ QW group and 21.9 [95% CI: 10.5, 40.4] events per 100 PY in the TCZ Q2W group) compared with the placebo arms (31.6 [95% CI: 17.7, 52.2] events per 100 PY in the PBO + 26 wk group), with the highest AE rate occurring in the PBO + 52 wk group (43.7 [95% CI: 27.0, 66.8] events per 100 PY). No deaths were reported during Part 1 of Study WA28119.

For several of the pre-specified AESI categories i.e. anaphylaxis, serious bleeding, serious myocardial infarction, serious gastrointestinal perforation, serious hepatic events, serious demyelinating events, there were no events observed in the trial.

The rates of infections, serious infections, injection site reactions, hypersensitivity reactions and stroke were low and occurred with comparable frequency in all treatment groups.

The rates of malignancies were numerically lower in the TCZ groups compared with the placebo groups, but with overlapping CIs. Overall, the rates of AESIs were lower in Study WA28119 (Part 1) compared with the reported rates in the GCA cohort from the MarketScan database. Of note, ICD-9 codes used for extracting AESIs from the MarketScan database may not map exactly with the MedDRA codes used in Study WA28119 (Part 1), hence no direct comparisons should be made.

Decreases from baseline were observed in mean and median neutrophil and platelet counts. Neutropenia (including “decreased neutrophil count”) was reported as an AE in 4 patients in the TCZ QW group and 2

patients in the TCZ Q2W group. Review of the clinical listings showed that there was no association between Grade 3 or 4 events of neutropenia and serious infections. Thrombocytopenia (including platelet count decreased) was reported as an AE in 2 patients in the TCZ Q2W group. Neither of the thrombocytopenia events was associated with a bleeding event.

No safety analyses based on demographic and other intrinsic factors (age, gender, race, weight, BMI, medical history) were performed.

Events that are consistent with glucocorticoid-induced toxicity from Part 1 of Study WA28119 were analysed retrospectively using criteria that were developed by the Sponsor prior to database lock. In Study WA28119, during the 52-week double-blind phase (Part 1), the proportion of patients who experienced any potentially glucocorticoid-induced toxicity events was numerically lower in both the TCZ groups (21.0% in TCZ QW and 18.4% in TCZ Q2W) compared with the placebo groups (28.0% in PBO + 26 wk and 29.4% in PBO + 52 wk). It should be noted that these data from Study WA28119 were analysed retrospectively and were not based on standard or pre-specified criteria. Additionally, the duration of the study was considered too short for some of these events to manifest.

The MarketScan data analysis showed a statistically significant increase in the likelihood (odds ratio = 1.17, 95% CI: 1.06, 1.29) of patients experiencing any glucocorticoid-related event associated with each 1 gram increase in cumulative glucocorticoid dose in the first year following diagnosis with GCA.

The proportion of AEs leading to withdrawal from TCZ/placebo treatment was 6.0% in the PBO + 26wk group and 11.0% and 10.2% in the TCZ groups. There were no such events in the PBO + 52wk group.

Data from the LTE phase (Part 2) of study WA28119 as well as data from the investigator-initiated trial (ML25676) are consistent with the data from Part 1 of study WA28119. Importantly no signals were observed in Part 2 of the study which precludes treatment beyond week 52.

These results demonstrate that the safety profile of TCZ SC (QW and Q2W) in GCA is comparable with the known the known safety profile in RA.

Background AESI rates and glucocorticoid induced toxicity in GCA (in absence of TCZ exposure) from the MarketScan analysis are presented to contextualize rates reported with TCZ treatment in Study WA28119 for some AESIS, overall, the rates of AESIs were lower in Study WA28119 (Part 1) compared with the reported rates in the GCA cohort from the MarketScan database.

2.5.2. Conclusions on clinical safety

The safety profile of TCZ 162 mg SC (QW and Q2W) in GCA is in line with the known safety profile in RA and no new safety concerns were identified.

The safety profile in the placebo groups was less favourable than in the i.e. a higher SAE rate was reported in the placebo groups.

The favourable safety profile of TCZ in GCA patients was also confirmed evaluating background AESI rates and glucocorticoid induced toxicity in GCA (in absence of TCZ exposure) from the MarketScan. These data indicate that rates of AESIs were lower in Study WA28119 (Part 1) compared with the reported rates in the GCA cohort from the MarketScan database.

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

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 21.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 21.0 with the following content:

Safety concerns

Summary of Ongoing Safety Concerns in Adults

Category	Safety Concern
Important Identified Risks	Serious infections
	Complications of diverticulitis
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Thrombocytopenia and the potential risk of bleeding
	Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity
	Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events
	Malignancies
	Demyelinating disorders
	Immunogenicity
Missing information	Elderly patients
	Pediatric patients
	Effects during pregnancy
	Hepatic impairment
	Renal impairment
	Combination with biologics
	Safety in patients <60 kg in switcher population
	Long-term safety in patients in the switcher patient population
Identified and potential interactions including food-drug and drug-drug interactions	CYP450 enzyme normalization

Summary of Ongoing Safety Concerns in Pediatric Patients

Category	Safety Concern
Important Identified Risks	Serious infections
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Skeletal development
	Immunogenicity
	Malignancies
	CYP450 enzyme normalization
Missing information	MAS in sJIA patients

Pharmacovigilance plan

Activity / Study title (category 3)*	Objectives	Safety concerns addressed	Status Planned, started, ongoing	Date for submission of interim or final reports (planned or actual)
WA22479 (British Society of Rheumatology Biologics Register [BSRBR])	Prospective observational cohort studies for safety data collection.	General safety profile of TCZ. Safety of TCZ SC in patients < 60 kg in the switcher population. Long-term safety in switcher patient population.	Ongoing	Routine updates to be provided in the scheduled PSURs. Final CSR Q3 2017
WA22480 (ARTIS) registry study	To provide long term safety data from the use of TCZ in Sweden for RA patients			
GA28719 (RABBIT)	The long-term observation of treatment with biologics in RA (RABBIT) in German biologics registry			
Pregnancy registry (GA28720 [OTIS])	To evaluate pregnancy outcomes for women exposed to TCZ during pregnancy			
Paediatric Registry (WA29358): Observational Safety and Effec-tiveness Study of Patients with	Collecting long term efficacy and safety data in PJIA treatment. The registry will address, but is not limited to, efficacy of 10 mg/kg for patients < 30 kg; impact of	Safety in pediatric patients	Ongoing	Final report date expected March 2025.

Activity / Study title (category 3)*	Objectives	Safety concerns addressed	Status Planned, started, ongoing	Date for submission of interim or final reports (planned or actual)
Polyarticular Juvenile Idiopathic Arthritis Treated with Tocilizumab	the RF status on efficacy of TCZ therapy; impact of TCZ therapy on the increased risk of atherosclerosis in RA patients, impact on of TCZ therapy growth development, influence on the occurrence / treatment of uveitis. and to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation			
WA28029	To evaluate decreased dose frequency in patients with sJIA who experience laboratory abnormalities during treatment with TCZ	Safety in pediatric patients	Ongoing	First Patient First Visit June 2013 Final CSR expected 2020
NP25737	A pharmacokinetic and safety study of TCZ in patients less than 2 years old with active sJIA	Safety profile in pediatric patients less than 2 years old	Ongoing	Final CSR expected November 2017
WA25204 (ENTRACTE)	A clinical outcomes study to evaluate the effects of IL-6 receptor blockade with to-cilizumab (TCZ) in compari-son with etanercept (ETA) on the rate of cardiovascular events in patients with moderate to severe rheumatoid arthritis (RA).	Cardiovascular events	Ongoing	Final CSR expected Q1 2017

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important Identified Risks		
Serious Infections	SPC IV Formulation: SPC Section 4.3 Contraindications Active, severe infections (see section 4.4) SPC section 4.4 Special warnings and precautions for use **Infections** Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including TCZ	<u>Patient Alert Card</u> To inform both the patient and health care providers that TCZ increases the risk of getting infections which can become serious if not treated and of the need for timely

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	(see section 4.8, Undesirable Effects). TCZ treatment should not be initiated in patients with active infections (see section 4.3). Administration of TCZ should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of TCZ in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, and interstitial lung disease which may predispose patients to infections. Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for moderate to severe RA, sJIA or pJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment. **Tuberculosis** As recommended for other biological treatments, RA, sJIA and pJIA patients should be screened for latent tuberculosis (TB) infection prior to starting TCZ therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating TCZ. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with TCZ.. SC Formulation SPC Section 4.3 Contraindications Active, severe infections (see section 4.4) SPC section 4.4 Special warnings and precautions for use **Infections** Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including TCZ (see section 4.8, Undesirable effects). TCZ treatment must not be initiated in patients with active infections (see section 4.3). Administration of TCZ should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of TCZ in patients with a	and appropriate diagnostic and therapeutic measures in case of the early signs of infections Patient Brochure To inform the patient of the risk of serious infections and and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide more detailed guidance to healthcare providers on the risk of serious infections

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	history of recurring or chronic infections or with underlying conditions (e.g.) diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections. Vigilance for the timely detection of serious infection is recommended for patients receiving immunosupressive agents such as TCZ for moderate to severe RA or GCA as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of tocilizumab on C reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment. **Tuberculosis** As recommended for other biological treatments, all patients should be screened for latent tuberculosis infection prior to starting TCZ therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating TCZ. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with TCZ IV Formulation: SPC section 4.8 Undesirable effects Adult population **RA:** **Infections** In the 6-month controlled studies the rate of all infections reported with tocilizumab 8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD group. In the long term exposure population, the overall rate of infections with TCZ was 108 events per 100 patient years exposure. In 6-month controlled clinical studies, the rate of serious infections with tocilizumab 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group. In the long term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported. **Interstitial Lung Disease** Impaired lung function may increase the risk for developing infections. There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes. Paediatric population **sJIA :** **Infections** In the 12 week controlled phase, the rate of all infections in the tocilizumab group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the ongoing open label extension phase (Part II), the overall rate of infections remained similar at 306.6 per 100 patient years. In the 12 week controlled phase, the rate of serious infections in the tocilizumab group was 11.5 per 100 patient years. At one year in the ongoing open label extension phase the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media. **pJIA:** **Infections** The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg tocilizumab (7.6%). SC Formulation: SPC section 4.8 Undesirable effects Adult population **RA:** The safety and immunogenicity observed for TCZ administered subcutaneous was consistent with the known safety profile of intravenous TCZ and no new or unexpected adverse drug reactions were observed (see Table 1).	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	GCA: **Infections** The rate of infection/serious infection events was balanced between the TCZ weekly group (200.2/9.7 events per 100 patient years) vs. placebo + 26 weeks prednisone taper (156.0/4.2 events per 100 patient years) and placebo + 52 weeks taper (210.2/12.5 events per 100 patient years) groups. **Patient Information Leaflet:** **IV Formulation :** Section 2. What you need to know before you are given TCZ • You are not to be given TCZ o if you have an active, severe infection. **SC Formulation:** Section 2. What you need to know before you use TCZ • Do not use TCZ o if you have an active, severe infection. **IV/SC Formulation** **Warnings and Precautions** If you have any kind of infection, short- or long-term, or if you often get infections. Tell your doctor immediately if you feel unwell. TCZ can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection. If you have had tuberculosis, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting TCZ. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately. Section 4 Possible serious side effects: tell a doctor straightaway. Infections: • fever and chills • mouth or skin blisters • stomach ache If you notice any of these, tell your doctor as soon as possible.	
Complications of diverticulitis	SPC SPC section 4.4 Special warnings and precautions for use **Complications of diverticulitis** Events of diverticular perforations as complications of diverticulitis have been reported uncommonly in patients treated with TCZ (see section 4.8). TCZ should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early	<u>Patient Alert Card</u> To inform both the patient and health care providers that patients using TCZ may develop complications of diverticulitis which can become serious

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	identification of diverticulitis which can be associated with gastrointestinal perforation. SPC section 4.8 Undesirable effects **Gastrointestinal Perforation** During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess. **Patient Information Leaflet:** Section 2 Warnings and precautions Talk to your doctor or nurse before using TCZ. If you have had intestinal ulcers or diverticulitis, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.	if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of such events. Patient Brochure To inform the patient of the risk of complications of diverticulitis and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide more detailed guidance to healthcare providers on the risk of complications of diverticulitis
Serious Hypersensitivity Reactions	SPC SPC Section 4.8 Undesirable effects: **Infusion Reactions** In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting. The rate of anaphylactic reactions (occurring in a total of 8/4,009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with *intravenous [IV Formulation only]* tocilizumab (see section 4.4). SPC section 4.4 Special warnings and precautions for use	Patient Alert Card To inform patients, parents or caregivers of pediatric patients, and health care providers that patients using TCZ may develop allergic reactions during or after the infusion. Patients who develop allergic reactions after the infusion should seek medical attention immediately. Patient Brochure To inform the patient of the risk of of serious hypersensitivity reactions nd provide additional guidance beyond that

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Hypersensitivity Reactions Serious hypersensitivity reactions, including anaphylaxis have been reported in association with TCZ (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous treatment with tocilizumab even if they have received premedication with steroids and antihistamines. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of TCZ should be stopped immediately, and appropriate therapy initiated and tocilizumab should be permanently discontinued. SPC Section 4.8 Undesirable effects Paediatric population sJIA : **Infusion Reactions** Infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled phase, 4% of patients from the tocilizumab group experienced events occurring during infusion. One event (angioedema) was considered serious and life threatening, and the patient was discontinued from study treatment. In the 12 week controlled phase, 16% of patients in the tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. At week 260, 12 patients had experienced 16 events during infusion giving a rate of events of 4.4 per 100 patient years. In the tocilizumab group, the events included, but were not limited to rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (< 1%) treated with tocilizumab during the controlled and up to and including the open label clinical trial. pJIA: **Infusion Reactions** In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occuring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8. No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.	provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of serious hypersensitivity reactions Rheumatoid Arthritis Dosing Guide To provide support to the patient and healthcare provider regarding dosing and administration instructions

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Patient Information Leaflet (IV formulation): Section 2 What you need to know before you are given TCZ. Warnings and precautions Talk to your doctor, or nurse before using TCZ: If you experience allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash during or after the infusion, then tell your doctor immediately. Patient Information Leaflet (SC formulation) : Section 2 What you need to know before you use TCZ Warnings and precautions Talk to your doctor, pharmacist or nurse before using TCZ. If you experience allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the injection, then tell your doctor immediately. Do not take the next dose until you have informed your doctor AND your doctor has told you to take the next dose if you have experienced any allergic reaction symptoms after TCZ administration. Section 4 POSSIBLE SIDE EFFECTS Common side effects Rash and itching, hives Allergic (hypersensitivity) reactions.	
Neutropenia	SPC SPC section 4.4 Special warnings and precautions for use **Haematological abnormalities** Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. In patients not previously treated with TCZ, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L. Caution should be exercised when considering initiation of TCZ treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µL). In patients who develop an ANC < 0.5 x 10^9/L or a platelet count < 50 x 10^3/µL, continued treatment is not recommended. Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with TCZ to date. In RA and GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2. SPC section 4.4 Special warnings and precautions for use (IV formulation) **Haematological abnormalities**	<u>Patient Brochure</u> To inform the patient of the risk of neutropenia and provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide guidance to healthcare providers on the risk of neutropenia

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2. SPC Section 4.8 Undesirable effects/Laboratory evaluations **Haematological abnormalities** **RA Patients** **Neutrophils** In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs. Infections with neutropenia have been reported. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials. Paediatric population **pJIA Patients** Neutrophils During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1 × 10^9/L occurred in 25% of patients. **sJIA Patients** Neutrophils During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1 x 10^9/L occurred in 7% of patients in the tocilizumab group, and no decreases in the placebo group. In the ongoing open label extension phase, decreases in neutrophil counts below 1 x 10^9/L, occurred in 15% of the tocilizumab group. **GCA Patients** Neutrophils During routine laboratory monitoring in the tocilizumab 12-month controlled clinical trial, a decrease in neutrophil count below 1 × 10^9/L occurred in 4% of patients in the tocilizumab subcutaneous weekly group. This was not observed in either of the placebo plus prednisone taper	

<table>
<tr><th>Safety concern</th><th>Routine risk minimization measures</th><th>Additional risk minimization measures</th></tr>
<tr><td></td><td>groups.

SPC section 4.2 Posology and method of administration
RA Patients
Dose adjustments due to laboratory abnormalities (see section 4.4) (IV formulation)
• Low absolute neutrophil count (ANC)
In patients not previously treated with TCZ, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L.
<table>
<tr><td>Laboratory Value (cells x 10^9/L)</td><td>Action</td></tr>
<tr><td>ANC > 1</td><td>Maintain dose</td></tr>
<tr><td>ANC
0.5 to 1</td><td>Interrupt TCZ dosing
When ANC increases > 1 x 10^9/ l resume TCZ at 4 mg/kg and increase to 8 mg/kg as clinically appropriate</td></tr>
<tr><td>ANC < 0.5</td><td>Discontinue TCZ</td></tr>
</table>
RA and GCA patients
Dose adjustments due to laboratory abnormalities (see section 4.4) (SC formulation)
<table>
<tr><td>Laboratory Value (cells x 10^9/L)</td><td>Action</td></tr>
<tr><td>ANC > 1</td><td>Maintain dose</td></tr>
<tr><td>ANC
0.5 to 1</td><td>Interrupt TCZ dosing
When ANC increases > 1 x 10^9/ l resume dosing every other week and increase to every week injection, as clinically appropriate.</td></tr>
<tr><td>ANC < 0.5</td><td>Discontinue TCZ</td></tr>
</table>
Paediatric patients:
sJIA Patients
Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual</td><td></td></tr>
</table>

<table>
<tr><th>Safety concern</th><th>Routine risk minimization measures</th><th>Additional risk minimization measures</th></tr>
<tr><td></td><td>patient.
• Low absolute neutrophil count (ANC)
<table>
<tr><td>Laboratory Value (cells x 10^9/L)</td><td>Action</td></tr>
<tr><td>ANC > 1</td><td>Maintain dose</td></tr>
<tr><td>ANC
0.5 to 1</td><td>Interrupt TCZ dosing
When ANC increases to > 1 x 10^9/ l resume TCZ.</td></tr>
<tr><td>ANC < 0.5</td><td>Discontinue TCZ
The decision to discontinue TCZ in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.</td></tr>
</table>
pJIA Patients
Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in pJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.
• Low absolute neutrophil count (ANC)
<table>
<tr><td>Laboratory Value (cells x 10^9/L)</td><td>Action</td></tr>
<tr><td>ANC > 1</td><td>Maintain dose</td></tr>
<tr><td>ANC
0.5 to 1</td><td>Interrupt TCZ dosing
When ANC increases to > 1 x 10^9/ l resume TCZ.</td></tr>
<tr><td>ANC < 0.5</td><td>Discontinue TCZ
The decision to discontinue TCZ in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.</td></tr>
</table>
Patient Information Leaflet
Section 4 POSSIBLE SIDE EFFECTS
Common side effects: … low white blood counts shown by blood tests (neutropenia, leucopenia)</td><td></td></tr>
<tr><td colspan="3">Important Potential Risks</td></tr>
<tr><td>Thrombocytopenia</td><td>SPC</td><td>Patient Brochure</td></tr>
</table>

Safety concern	Routine risk minimization measures	Additional risk minimization measures
and the potential risk of bleeding	SPC section 4.4 Special warnings and precautions for use **RA** **Haematological abnormalities** Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2. **GCA** **Haematological abnormalities** In GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts (see section 4.2). SPC Section 4.8 Undesirable effects **Haematological abnormalities** Platelets In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/ µl occurred in 1.7% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials. **GCA** **Haematological abnormalities** Platelets During routine laboratory monitoring in the tocilizumab 12 month controlled clinical trial, one patient (1%, 1/100) in the tocilizumab subcutaneous weekly group had a single transient occurence of decrease in platelet count to <100 × 10^3 / µL without associated bleeding events. A decrease in platelet count below 100 × 10^3 / µL was not observed in either of the placebo plus prednisone taper groups.	To inform the patient of the risk of thrombocytopenia and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of thrombocytopenia

<table>
<tr><th>Safety concern</th><th>Routine risk minimization measures</th><th>Additional risk minimization measures</th></tr>
<tr><td></td><td>SPC section 4.2 Posology and method of administration (IV formulation)

Dose adjustments due to laboratory abnormalities
(see section 4.4)

• Low platelet count
<table>
<tr><td>Laboratory Value (cells x 10^3/ µL)</td><td>Action</td></tr>
<tr><td>50 to 100</td><td>Interrupt TCZ dosing
When platelet count > 100 x 10^3/ µL r
as clinically appropriate</td></tr>
<tr><td>< 50</td><td>Discontinue TCZ.</td></tr>
</table>
RA and GCA
SPC section 4.2 Posology and method of administration (SC formulation)
Dose adjustments due to laboratory abnormalities (see section 4.4)
• Low platelet count
<table>
<tr><td>Laboratory Value (cells x 10^3/ µl)</td><td>Action</td></tr>
<tr><td>50 to 100</td><td>Interrupt TCZ dosing.
When platelet count > 100 x 10^3/ µl re
to every week injection as clinically ap</td></tr>
<tr><td>< 50</td><td>Discontinue TCZ.</td></tr>
</table>
Paediatric patients:
SPC section 4.4 Special warnings and precautionsfor use (IV formulation)
Haematological abnormalities
In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2.
SPC section 4.8 Undesirable effects (IV formulation)
Platelets
sJIA Patients
During routine laboratory monitoring in the 12 week controlled phase, 3% of patients in the placebo group and 1% in the tocilizumab group had a decrease in platelet count to ≤ 100 x 10^3/µl.
In the completed open label extension phase, decreases in platelet counts below 100 x 10^3/µl, occurred in 3.6% of</td><td></td></tr>
</table>

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	patients in the tocilizumab group, without associated bleeding events.pJIA Patients During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to ≤ 50 × 10^3/µL without associated bleeding events.	
Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity	SPC SPC section 4.4 Special warnings and precautions for use **RA** **Active hepatic disease and hepatic impairment** Treatment with TCZ, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8). **Hepatic transaminase elevations** In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with TCZ treatment, without progression to hepatic injury (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with TCZ. When clinically indicated, other liver function tests including bilirubin should be considered. Caution should be exercised when considering initiation of TCZ treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended. In RA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, TCZ treatment should be interrupted. **GCA** **Hepatic transaminase elevations** In GCA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, TCZ treatment should be interrupted. SPC section 4.8 Undesirable effects **RA**	Patient Brochure To inform the patient of the risk of liver enzyme and bilirubin elevations and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Hepatic transaminase elevations During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs. The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 2 x ULN. During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials. **GCA** **Hepatic transaminase elevations** During routine laboratory monitoring in the TCZ 12 month controlled clinical trial, elevation in ALT ≥3 x ULN occurred in 3% of patients in the TCZ SC QW compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 week prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the TCZ SC QW group, compared to no patients in either of the placebo plus prednisone taper groups. SPC section 4.2 Posology and method of administration (IV formulation) Dose adjustments due to laboratory abnormalities (see section 4.4) **Liver enzyme abnormalities** Laboratory Value | > 1 to 3 x Upper Limit of Normal | Modify the dose of the concomitant MT For persistent increases in this range, re	

Safety concern	Routine risk minimization measures		Additional risk minimization measures
	(ULN)	ALT or AST have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate	
	> 3 to 5 x ULN (confirmed by repeat testing, see section 4.4).	Interrupt TCZ dosing until < 3 x ULN and follow recommendations above ULN For persistent increases > 3 x ULN, discontinue TCZ	
	> 5 x ULN	Discontinue TCZ	

SPC section 4.2 Posology and method of administration (SC formulation)

RA and GCA

Dose adjustments due to laboratory abnormalities (see section 4.4)

Liver enzyme abnormalities

Laboratory Value	
> 1 to 3 x Upper Limit of Normal (ULN)	Dose modify concomitant DMARDs (RA appropriate. For persistent increases in this range, injection or interrupt TCZ until ALT or A Restart with weekly or every other wee
> 3 to 5 x ULN	Interrupt TCZ dosing until < 3 x ULN a ULN. For persistent increases > 3 x ULN (cor TCZ.
> 5 x ULN	Discontinue TCZ.

Peadiatric Patients

SPC section 4.4 Special warnings and precautions for use

Hepatic transaminase elevations

In sJIA and pJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.

sJIA Patients

SPC section 4.8 Undesirable effects

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST ≥ 3 x ULN occurred in 5% and 3% of patients, respectively, in the tocilizumab group, and 0% in the placebo group.

In the completed open label extension phase, elevation in ALT or AST ≥ 3 x ULN occurred in 5% and 3% of patients, respectively, in the tocilizumab group, and 0% in the placebo group.

In the completed open label extension phase, elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients,

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	respectively, in the tocilizumab group. **pJIA Patients** During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥ 3xULN occurred in 3.7% and <1% of patients, respectively. Patient Information Leaflet (IV formulation) Section 2 Warning and precautions If you have liver disease, tell your doctor. Before you use TCZ, your doctor may do a blood test to measure your liver function. Patient Information Leaflet (SC formulation) Section 2 Warning and precautions If you have liver disease, tell your doctor. Before you use TCZ, your doctor may do a blood test to measure your liver function.	
Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	SPC SPC section 4.4 Special warnings and precautions for use **Lipid parameters** Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with tocilizumab (see section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents. **RA Patients** In RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of TCZ therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. **Cardiovascular Risk** RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care. **GCA Patients** In GCA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of TCZ therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. SPC section 4.8 Undesirable effects **Lipid parameters** During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving TCZ in clinical	Patient Brochure To inform the patient of the risk of elevated lipid levels and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of elevated lipid levels

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ l. Elevations in lipid parameters responded to treatment with lipid-lowering agents. During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials. **GCA patients** **Lipid parameters** During routine laboratory monitoring in the tocilizumab 12-month controlled clinical trial, 25% of patients experienced elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 47% experiencing an increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the tocilizumab subcutaneous weekly group. **RA Patients** SPC section 4.8 Undesirable effects Hypertension reported as a common ADR. **Paediatric Patients** SPC section 4.4 Special warnings and precautions for use **Lipid parameters** In sJIA, pJIA and RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of TCZ therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. SPC section 4.8 Undesirable effects **Lipid parameters** sJIA: During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol > 1.5 x ULN to 2 x ULN occurred in 1.5% of the tocilizumab group and none in the placebo group. Elevation in LDL > 1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the tocilizumab group, and in 0% of the placebo group. In the completed open label extension phase, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled phase data. pJIA: During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x ULN in one patient (0.5%). Patient Information Leaflet Section 2 Warnings and precautions If you have cardiovascular risk factors such as raised blood pressure and raised cholesterol levels, tell your doctor. These	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	factors need to be monitored while receiving TCZ.	
Malignancies	SPC SPC section 4.4 Special warnings and precautions for use **RA Patients** **Malignancy** The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. SPC section 4.8 Undesirable effects **Malignancies** The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.	Patient Brochure To inform the patient of the risk of malignancies and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of malignancies
Demyelinating disorders	SPC SPC section 4.4 Special warnings and precautions for use **Neurological disorders** Physicians should be vigilant for symptoms potentially indicative of new onset central demyelinating disorders. The potential for central demyelination with TCZ is currently unknown.	Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of demyelinating disorders
Immunogenicity	SPC SPC section 4 .8. Undesirable effects **RA Patients** **Immunogenicity** A total of 2,876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies. In SC-I, a total of 625 patients treated with tocilizumab 162 mg weekly were tested for anti-tocilizumab antibodies in the 6-month controlled period. Five patients (0.8%) developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies. One patient was tested positive for IgE isotype (0.2%). In SC-II, a total of 434 patients treated with tocilizumab 162mg every other weekly were tested for anti-tocilizumab antibodies in the 6-month controlled period. Seven patients (1.6%) developed positive anti-tocilizumab antibodies; of these, six (1.4%) developed neutralizing anti-tocilizumab antibodies. Four patients were tested positive for IgE isotype (0.9%).	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	No correlation of antibody development to clinical response or adverse events was observed. SPC section 4 .8. Undesirable effects **GCA Patients** **Immunogenicity** In the tocilizumab subcutaneous weekly group, one patient 1.1% (1/95) developed positive neutralizing anti-tocilizumab antibodies, though not of the IgE isotype. This patient did not develop a hypersensitivity reaction or injection site reaction. SPC section 4 .8. Undesirable effects (IV formulation) **sJIA Patients** **Immunogenicity** All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-tocilizumab antibody formation might be underestimated because of interference of tocilizumab with the assay and higher drug concentration observed in children compared to adults. **pJIA Patients** One patient in the 10 mg/kg < 30kg group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.	
Skeletal development (in paediatric patients)	None proposed	Not applicable
Missing Information		
CYP450 enzyme normalization	Routine risk minimization by means of labelling: SPC SPC section 4.5 Interaction with other medicinal products and other forms of interaction Interaction studies have only been performed in adults. Concomitant administration of a single dose of 10 mg/kg tocilizumab with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on tocilizumab clearance in RA patients. In the GCA patients, no effect of cumulative corticosteroid dose on TCZ exposure was observed. The expression of hepatic CYP450 enzymes is suppressed by the cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as tocilizumab,	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	is introduced. In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. Tocilizumab normalises expression of these enzymes. In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of tocilizumab, to the level similar to, or slightly higher than, those observed in healthy subjects. When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy. Patient Information Leaflet (IV formulation) Section 2 What you need to know before you use TCZ Other medicines and TCZ Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. TCZ can affect the way some medicines work, and the dose of these may require adjustment. You, and parents/guardians of sJIA and pJIA patients should tell your doctor if you are using medicines containing any of the following active substances: • atorvastatin, used to reduce cholesterol levels • calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure • theophylline, used to treat asthma • warfarin/phenprocoumon, used as a blood thinning agent • phenytoin, used to treat convulsions • ciclosporin, used to suppress your immune system during organ transplants • benzodiazepines (e.g., temazepam), used to relieve anxiety Patient Information Leaflet (SC formulation) Section 2 What you need to know before you use TCZ Other medicines and TCZ Tell your doctor if you are taking, have recently taken or might take any other medicines. TCZ can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, tell your doctor:	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	• atorvastatin, used to reduce cholesterol levels • calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure • theophylline, used to treat asthma • warfarin/phenprocoumon, used as a blood thinning agent • phenytoin, used to treat convulsions • ciclosporin, used to suppress your immune system during organ transplants • benzodiazepines (e.g. temazepam), used to relieve anxiety	
Macrophage Activation Syndrome in sJIA Patients	SPC Section 4.4 Special warnings and precautions for use (IV formulation) **Paediatric population** Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS. Patient Information Leaflet What you need to know before you are given TCZ Section 2 Warnings and precautions If you have a history of macrophage activation syndrome, which is the activation and uncontrolled proliferation of specific blood cells, tell your doctor. Your doctor will have to decide if you can still be given TCZ.	Patient Alert Card To inform the patient of the risk of MAS and provide additional guidance beyond that provided in the PIL
Pediatric patients	SPC Section 4.2 Posology and method of administration **Special populations** **sJIA Patients** The safety and efficacy of TCZ in children below 2 years of age has not been established. The recommended posology is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	patient [Tables of dose modification recommendations] Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in sJIA patients. Available data suggest that clinical improvement is observed within 6 weeks of initiation of reatment with TCZ. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe. Section 4.4 Special warnings and precautions for use Paediatric population sJIA Patients Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS. Section 4.5: Interactions with other medicinal products Pediatric population Interaction studies have only been performed in adults. PIL What TCZ is and what it is used for and Children and Adolescents TCZ is not recommended for use in children younger than 2 years of age. Children with SJIA In general, the side effects in sJIA patients were similar in type to those seen in RA patients, listed above.	
Elderly Patients	SPC SPC section 4.2 Posology and Method of Administration Special populations *Elderly Patients* No dose adjustment is required in patients aged 65 years and older.	None proposed
Effects during pregnancy	SPC SPC section 4.6 Fertility, Pregnancy and lactation Women of childbearing potential Women of childbearing potential must use effective contraception during and up to 3 months after treatment. Pregnancy There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown. TCZ should not be used during pregnancy unless clearly necessary. Breast-feeding It is unknown whether tocilizumab is excreted in human breast milk. The excretion of TCZ in milk has not been studied in animals. A decision on whether to continue/discontinue	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	breast feeding or to continue/discontinue therapy with TCZ should be made taking into account the benefit of breast feeding to the child and the benefit of TCZ therapy to the woman. Fertility Available non-clinical data do not suggest an effect on fertility under TCZ treatment. Patient Information Leaflet Section 2 Pregnancy, breast feeding and fertility TCZ is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant. Stop breast-feeding if you are to be given TCZ, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether TCZ is passed into breast milk.	
Hepatic impairment	SPC SPC section 4.2 Posology and Method of Administration. Special populations Hepatic Impairment TCZ has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made. SPC section 4.4 Special warnings and precautions for use Active hepatic disease and hepatic impairment Treatment with TCZ, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8). SPC section 5.2 Pharmacokinetic properties Special populations Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted. Patient Information Leaflet Section 2 Warnings and precautions Talk to your doctor, pharmacist, or nurse before using TCZ: If you have liver disease, tell your doctor. Before you use TCZ, your doctor may do a blood test to measure your liver function.	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Renal Impairment	SPC IV Formulation SPC section 4.2 Posology and Method of Administration Special populations Renal Impairment No dose adjustment is required in patients with mild renal impairment. TCZ has not been studied in patients with moderate to severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients. SPC Section 5.2 Pharmacokinetic properties Special populations Renal Impairment No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the phase 3 RA and GCA study population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on the Cockcroft-Gault formula < 80 mL/min and ≥ 50 mL/min) did not impact the pharmacokinetics of tocilizumab. SPC SC Formulation SPC section 4.2 Posology and Method of Administration Special populations Renal Impairment No dose adjustment is required in patients with mild or moderate renal impairment. TCZ has not been studied in patients with severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients. SPC section 5.2 Pharmacokinetic properties Special populations Renal Impairment No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab. Approximately one-third of the patients in the GCA study had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on TCZ exposure was noted in these patients. No dose adjustment is required in patients with mild or moderate renal impairment. Patient Information Leaflet	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Section 2 Warnings and precautions Talk to your doctor, pharmacist, or nurse before using TCZ: If you have moderate to severe kidney function problems, your doctor will monitor you.	
Combination with biologics	SPC SPC section 4.4 Special warnings and precautions for use (IV formulation) Combination with TNF antagonists There is no experience with the use of TCZ with TNF antagonists or other biological treatments for RA sJIA or pJIA patients. TCZ is not recommended for use with other biological agents. SPC section 4.4 Special warnings and precautions for use (SC formulation) Combination with TNF antagonists There is no experience with the use of TCZ with TNF antagonists or other biological treatments for RA, sJIA or pJIA patients. TCZ is not recommended for use with other biological agents. Patient Information Leaflet (IV formulation) Section 2 Warnings and precautions Other medicines and TCZ Due to lack of clinical experience, TCZ is not recommended for use with other biological medicines for the treatment of RA, sJIA or pJIA. Patient Information Leaflet (SC formulation) Section 2 Warnings and precautions Other medicines and TCZ Due to lack of clinical experience, TCZ is not recommended for use with other biological medicines for the treatment of RA.	None proposed
Safety in patients <60 kg in switcher population	SPC SPC section 5.1 Pharmacodynamic properties <u>Subcutaneous Use</u> <u>Clinical efficacy</u> Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.	None proposed
Long-term safety in the switcher patient population	SPC SPC section 5.1 Pharmacodynamic properties <u>Subcutaneous Use</u>	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Clinical efficacy Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to RoActemra 162 mg solution for subcutaneous injection in a pre-filled syringe. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

RoActemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

3.1.2. Available therapies and unmet medical need

Glucocorticoids (GC) are the mainstay of treatment for GCA and are typically administered in the form of oral prednisone/prednisolone, although some physicians use pulsed intravenous (IV) glucocorticoids in patients presenting with visual loss. Although glucocorticoids are highly effective at inducing remission of systemic inflammation and preventing acute damage (e.g., blindness), this comes with a high toxicity burden, with approximately 80% of patients suffering GC-related adverse clinical events at 10-year follow-up (Proven et al. 2003). In addition, GC are not as effective at maintaining remission, with many patients (up to 50%) experiencing relapse or flare-up of symptoms during reduction or discontinuation of glucocorticoids (Proven et al. 2003). Other agents, including azathioprine, cyclophosphamide, methotrexate (MTX), infliximab, and etanercept, have shown conflicting or no evidence of benefit in the treatment of GCA. Also, MTX is used inconsistently as standard of care for glucocorticoid-sparing in relapsing patients. More recently, limited efficacy in the treatment of GCA has been demonstrated with the use of combination treatment with abatacept and prednisone (Langford et al. 2015).

3.1.3. Main clinical studies

Data to support the efficacy of tocilizumab (also known as RO4877533 and TCZ) in adult patients with giant cell arteritis (GCA or temporal arteritis) are provided from the pivotal Phase III trial (Study WA28119; GiACTA). Study WA28119 was designed to evaluate the efficacy of TCZ plus glucocorticoid treatment compared to treatment with glucocorticoids alone in new-onset and relapsing patients with GCA, as well as to evaluate the safety profile of TCZ treatment in this patient population. The study includes a 52-week blinded period (Part 1) followed by a 104-week open-label period (Part 2), with a total study duration of 156 weeks.

3.2. Favourable effects

The primary endpoint, superiority of each of the TCZ arms (with 26 week prednisone tapering) over PBO with 26 week tapering, was met. Sustained remission at Week 52 was achieved in 56.0% of patients in the TCZ QW group, 53.1% of patients in the TCZ Q2W group and 14.0% of patients in the PBO + 26 wk group. The difference in the percentage of responders between the TCZ QW group and placebo was 42.0% (99.5% CI: 18.0 to 66.0), with an associated p-value of < 0.0001. The difference in the percentage of responders between the TCZ Q2W dose group and placebo was 39.1% (99.5% CI: 12.5 to 65.7), with a p-value of < 0.0001.

The key secondary efficacy endpoint was the proportion of patients in sustained remission at Week 52 in the TCZ groups in combination with a 26-week prednisone taper compared with placebo in combination with a 52-week prednisone taper. Both the TCZ QW and TCZ Q2W dose groups met non-inferiority. In post hoc analyses subsequently superiority to placebo was shown with regard to the key secondary endpoint. Sustained remission at Week 52 was achieved by 56.0% of patients in the TCZ QW group, 53.1% of patients in the TCZ Q2W group and 17.6% of patients in the PBO + 52 wk group. The difference in the percentage of responders in the TCZ QW group versus the PBO + 52 wk group was 38.4% (99.5% CI: 17.9 to 58.8) and the difference in the percentage of responders in the TCZ Q2W group versus the PBO + 52 wk group was 35.4% (99.5% CI: 10.4 to 60.4). The lower boundaries of the 99.5% CIs for both TCZ dose groups were greater than the non-inferiority margin of -22.5%, meeting the criteria for non-inferiority.

A statistically significantly lower cumulative prednisone dose to Week 52 in both the TCZ QW and TCZ Q2W treatment groups in combination with a 26 week prednisone taper period when compared to placebo was reported.

3.3. Uncertainties and limitations about favourable effects

The effect on entire course of GCA episode including early remission which should be the primary goal of any GCA treatment could not be evaluated with the current protocol.

TCZ monotherapy was not investigated in the clinical studies.

Data from the LTE part of study WA28119 suggest that in the TCZ groups a higher incidence of flares were observed after stopped their TCZ treatment at 52 weeks than in the placebo groups. A rebound effect cannot be excluded.

3.4. Unfavourable effect

The unfavourable effects of TCZ in the treatment of patients with GCA are consistent with the known safety profile of TCZ and include infections, injection site reactions, immunogenicity, haematological abnormalities, decrease in platelet count, and elevation in hepatic transaminase and lipid parameters.

3.5. Uncertainties and limitations about unfavourable effects

The numbers of patients contributing to efficacy and safety in GCA patients are relative small.

3.6. Effects Table

Table 37 - Effects Table for RoaActemra (indication: GCA]

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Sustained remission at wk 52	Proportion of patients in sustained remission at Week 52 treated with TCZ (QW or Q2W) or placebo in combination with 26 weeks prednisone taper regimen	N (%)	TCZ 162mg QW + 26 week prednisone taper; n=100 56% TCZ 162mg Q2W + 26 week prednisone taper, n=50 53.1%	PBO QW + 26 week prednisone taper n = 50 14%	The difference in the percentage of responders between the TCZ QW group and placebo was 42.0% (99.5% CI: 18.0 to 66.0), p-value of < 0.0001 The difference in the percentage of responders between the TCZ Q2W dose group and placebo was 39.1% (99.5% CI: 12.5 to 65.7), p-value of < 0.0001.	
Sustained remission at wk 52	Proportion of patients in sustained remission at Week 52 treated with TCZ (QW or Q2W) in combination with 26 weeks prednisone taper regimen or placebo in combination with 52 weeks prednisone taper regimen		TCZ 162mg QW + 26 week prednisone taper, n=100 56% TCZ 162mg Q2W + 26 week prednisone taper, n=50 53.1%	PBO QW + 52 week prednisone taper n = 50 17.6%	The difference in the percentage of responders in the TCZ QW group versus the PBO + 52 wk group was 38.4% (99.5% CI: 17.9 to 58.8) The difference in the percentage of responders in the TCZ Q2W group versus the PBO + 52 wk group was 35.4% (99.5% CI: 10.4 to 60.4)	
Unfavourable Effects						
SAE	Serious adverse events	Rate/ 100 PY	TCZ QW + 26 wk prednisone 29,1 TCZ Q2W + 26 wk prednisone 21.9	PBO QW + 26 wk prednisone 31,6 PBO QW + 52 wk prednisone		

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
				43.7		
Infections	AESI	Rate/ 100 PY	TCZ QW + 26 wk prednisone 200 TCZ Q2W + 26 wk prednisone 160	PBO QW + 26 wk prednisone 156 PBO QW + 52 wk prednisone 210		
Serious infection	AESI		TCZ QW + 26 wk prednisone 9.7 TCZ Q2W + 26 wk prednisone 4.4	PBO QW + 26 wk prednisone 4.2 PBO QW + 52 wk prednisone 12.5		
Injection site reactions	AESI		TCZ QW + 26 wk prednisone 7.5 TCZ Q2W + 26 wk prednisone 15.4	PBO QW + 26 wk prednisone 10.5 PBO QW + 52 wk prednisone 2.1		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint of the sustained remission at week 52 is clinically meaningful. TCZ 162 mg SC QW and Q2W with 26 week prednisone tapering regimen was superior to placebo in combination with a 26 wk or 52 wk resp. prednisone tapering regime and are effective at maintaining remission in patients with GCA.

Uncertainties with regard to maintenance of the remission after week 52 i.e. after stopping TCZ regimen exist, since preliminary data from the LTE part might indicate a rebound. The final WA28119 study report will be submitted by Q4 2018, where a possible rebound effect can be further re-assessed based on new data. This long term data will allow a proper assessment of the long-term efficacy i.e. maintenance of efficacy and safety. The MAH has committed to state the lack of data in the RMP under missing information. The final CSR and updated RMP will be submitted by Q1 2019.

Effect on entire course of GCA episode including early remission which should be the primary goal of any GCA treatment could not be directly evaluated with the current protocol.

However, data from the WA28119 study demonstrate a superior treatment effect of TCZ at 52 weeks, but also show an impact on treatment response as early as Week 1 after initiation of TCZ treatment. Thus, the differences in efficacy across groups were present at the earliest possible time points for assessment. These exploratory findings provide evidence on the efficacy of TCZ in establishing early disease control, even though this was not the principal aim of study WA28119.

Importantly patients in both TCZ groups had a significantly lower cumulative prednisone consumption (including all taper prednisone, escape therapy and commercial concomitant prednisone) than patients in the placebo arms. The lower cumulative prednisone dose to Week 52 in both TCZ groups as compared to the placebo groups might have contributed to the more favourable safety profile under TCZ treatment (e.g. less SAE's) compared to placebo.

RoActemra is intended to be used in combination with a tapering course of glucocorticoids. However, RoActemra can be used alone following discontinuation of glucocorticoids. Appropriate guidance has been included in section 4.2 of the SmPC.

The favourable safety profile of TCZ in GCA patients was also confirmed evaluating background AESI rates and glucocorticoid induced toxicity in GCA (in absence of TCZ exposure) from the MarketScan. These data indicate that rates of AESIs were lower in Study WA28119 (Part 1) compared with the reported rates in the GCA cohort from the MarketScan database.

3.7.2. Balance of benefits and risks

Sustained remission at week 52 was achieved under both TCZ regimens in combination with a 26 prednisone tapering regimen. TCZ was superior to placebo in combination with a 26 wk or 52 wk resp. prednisone tapering regime. Altogether the patients in both TCZ groups had a significant lower cumulative prednisone consumption (including all taper prednisone, escape therapy and commercial concomitant prednisone) than patients in the placebo arms. This contributes largely to a better safety profile in TCZ treated patients compared to patients treated with prednisone alone. Considering the age group of the target population (> 50 years) the favourable safety profile is an important factor.

3.8. Conclusions

The overall B/R of RoActemra is positive.

4. Recommendations

Outcome

Based on the review of the submitted 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	Type II	I, II and III

	approved one		

Extension of indication to include treatment of giant cell arteritis in adult patients for the subcutaneous formulation of RoActemra based on the Phase III study WA28119 (GiACTA). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect information relevant to this indication. The Package Leaflet is updated in accordance.

The Marketing Authorisation Holder took the opportunity to make administrative changes to Sections 4.6 and 5.3 of the SmPC.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and to the Risk Management Plan (RMP).

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;

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics

- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
    - The product must not be given to patients with active or suspected infection
    - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Serious injection/infusion reaction and their management
- Serious hypersensitivity reactions and their management
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Diagnosis of Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion reactions
    - Preparation of injection/infusion
    - Infusion rate
- Monitoring of the patient for injection/infusion reactions
- Reporting of serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet (with instructions for use for SC)
- Patient alert card

- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
- to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.
- to address the risk of allergic reactions.

These conditions do reflect the advice received from the PRAC.

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 giant cell arteritis in adult patients for the subcutaneous formulation of RoActemra based on the Phase III study WA28119 (GiACTA). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect information relevant to this indication. The Package Leaflet is updated in accordance.

The Marketing Authorisation Holder took the opportunity to make administrative changes to Sections 4.6 and 5.3 of the SmPC. The Package Leaflet is updated in accordance. Furthermore, the updated RMP version 21.0 has been agreed.

Summary

Please refer to the scientific discussion RoActemra EMEA/H/C/000955/II/0066.