Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Tocilizumab (rch)

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

First round report: 19 April 2017
Second round report: 6 July 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

1. List of abbreviations

Abbreviation	Meaning
AAR52	Annualised relapse rate up to Week 52
ACR	American College Of Rheumatologists
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve (mg/mL. Day)
AUC,ss	Area under the concentration-time curve at steady state (mg/mL Day)
AUCτ	Area under the concentration-time curve over dosing interval (mg/mL Day)
BLQ	Below the limit of quantitation
BMI	Body Mass Index (kg/m^2)
BQL	Below the quantification limit
BSR/BHPR	British Society For Rheumatology/British Health Professionals In Rheumatology
Cave8	Individual predicted average concentration up to Qeek 8 from treatment start
CCD	Cumulative corticosteroid dose
CI	Confidence interval
CL	Non-specific time-independent clearance (L/Day)
C_{max}	Maximum drug concentration (mg/mL)
C_{max},ss	Maximum drug concentration (mg/mL) at steady state
CPH	Cox proportional hazards
CRP	C-reactive protein

Abbreviation	Meaning
CTA	Computed Tomography Angiography
C_{trough}	Trough Drug Concentration (Mg/Ml)
$C_{trough,ss}$	Trough Drug Concentration (Mg/Ml) At Steady State
$C_{trough}52$	Steady-State Trough Concentration At Week 52
CV	Coefficient Of Variation
CWRES	Conditional Weighted Residuals
DV	Observed Tocilizumab Concentrations
ELISA	Enzyme-Linked Immunosorbent Assay
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
Fsc	Injection Site On Bioavailability
GCA	Giant Cell Arteritis
GI	Gastrointestinal
h	Hour/S
IBD	International Birth Date
IgG	Immunoglobulin G
II	Infections And Infestations
IL-6	Interleukin-6
IND	Investigational New Drug
IPRED	Individual Prediction
ITT	Intent-To-Treat
IV	Intravenous

Abbreviation	Meaning
ka	Absorption Rate Constant
LDL	Low-Density Lipoprotein
MCS	Mental Component Scores
mIL-6R	Membrane-bound interleukin-6 receptor
min	Minute(s)
MRA	Magnetic resonance angiography
NPDE	Normalised prediction distribution errors
OFV	Objective function value
PBRERs	Periodic Benefit-Risk Evaluation Reports
PBO	Placebo
PCS	Physical Component Score
PD	Pharmacodynamics
PET-CT	Positron emission tomography-computed tomography
PGA-VAS	Patient Global Assessment – Visual Analog Scale
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMR	Polymyalgia rheumatica
popPK	Population pharmacokinetics
PRED	Population predictions
PSUR	Periodic Safety Update Report
Q	Inter-compartmental clearance
Q2W	Every other week
QW	Weekly
RA	Rheumatoid arthritis
REMI52	Remission up to Week 52
SAE	Serious adverse event

Abbreviation	Meaning
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	Short-Form 36 (Questionnaire)
sIL-6R	Soluble interleukin-6 receptor
sJIA	Systemic juvenile idiopathic arthritis
$t_{1/2}$	Half-life
$t_{1/2}$, term	Terminal half-life
$t_{1/2}$,eff	Effective half-life
TAB	Temporal artery biopsy
TAD	Time after dose
TCZ	Tocilizumab
TFF	Time to flare
Vc	Central volume
Vp	Peripheral volume
VPC	Visual Predictive Check

2. Submission details

2.1. Identifying information

Submission number	PM-2016-03548-1-3
Sponsor	Roche Products Pvt Ltd.
Trade name	Actemra
Active substance	Tocilizumab (rch)

2.2. Submission type

This is an application to register a new indication for Actemra (tocilizumab, rch).

2.3. Drug class and therapeutic indication

Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass which binds to human interleukin 6 (IL-6) receptors.

The proposed new indication statement is:

> *Giant Cell Arteritis (SC formulation only): Actemra is indicated for the treatment of giant cell arteritis (GCA) in adult patients.*

The currently approved indications are:

> ***Rheumatoid Arthritis (IV and SC formulations):*** *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs.*
>
> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see CLINICAL TRIALS) in combination with MTX in those not previously treated with MTX.*
>
> *In the two groups of patients above, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*
>
> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by Xray, when given in combination with methotrexate.*
>
> ***Polyarticular Juvenile Idiopathic Arthritis (IV formulation only):*** *Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate (MTX). Actemra can be given alone or in combination with MTX.*
>
> ***Systemic Juvenile Idiopathic Arthritis (IV formulation only):*** *Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or in combination with methotrexate (MTX).*

2.4. Dosage forms and strengths

The currently available dosage forms for the other approved indications are:

- 80 mg/4 mL injection concentrated vial (AUST R 149403)
- 100 mg/10 mL injection concentrated vial (AUST R 149404)
- 400 mg/20 mL injection concentrated vial (AUST R 149402)
- 162 mg/0.9 mL solution for injection pre-filled syringe (AUST R 234034).

The proposed dosage form for the extended indication in GCA is as follows:

> Actemra tocilizumab, rch 162 mg/0.9 mL solution for injection pre-filled syringe (AUST R 234034). No new dosage form is proposed for the extended indication.

2.5. Dosage and administration

There were no changes to 'Dosage and administration' sections for the other indications which are already approved in Australia.

The following information on 'Dosage and administration' for the new proposed indication of GCA was provided in the proposed Australian PI:

> Treatment should be initiated by healthcare professionals experienced not only in the diagnosis and treatment of RA, GCA, pJIA or sJIA but also in the use of biological therapies for these conditions. For pJIA and sJIA treatment should be prescribed by medical practitioners experienced in the management of these conditions.
>
> For adult patients with RA, Actemra may be administered as an IV infusion or an SC injection.
>
> For adult patients with GCA, Actemra is administered as a SC injection.
>
> For patients with pJIA and sJIA, Actemra is administered as an IV infusion. For the treatment of pJIA and sJIA Actemra should be administered in a hospital setting with immediate access to the necessary medical personnel and full resuscitation facilities (see PRECAUTIONS - Hypersensitivity Reactions, ADVERSE EFFECTS - Infusion Reactions and Post-marketing Experience). Subcutaneous Actemra is only indicated in the treatment of patients with adult RA and GCA and is not indicated for the treatment of patients with pJIA or sJIA.
>
> ***Giant Cell Arteritis (SC formulation only)***
> The recommended dose of Actemra for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids. Actemra can be used alone following discontinuation of glucocorticoids. In the event of patients experiencing a relapse of GCA during the course of Actemra therapy, the treating physician should consider re-introducing and/or escalating the dose of concomitant glucocorticoids (or restarting glucocorticoid therapy if it has been discontinued) according to best medical judgement/treatment guidelines.
>
> Actemra SC formulation is not intended for IV administration. At least the first injection must be performed under the supervision of a qualified healthcare professional, in a healthcare facility with the necessary medical treatment available (including resuscitation equipment, protocols and appropriately trained personnel) in case of the need to initiate management of serious hypersensitivity reactions, including anaphylaxis. The patient must be closely monitored during the injection and afterwards for any signs and symptoms of a hypersensitivity reaction.

Subcutaneous Actemra is intended for use under the guidance and supervision of the patient's treating physician. After proper training in injection technique, patients may self-inject with Actemra only if their treating physician determines that it is appropriate and is satisfied that the patient can safely self-inject in the home environment and with medical follow-up as necessary. Assess suitability of patient for SC home use and instruct patients to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose.

Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see PRECAUTIONS, Hypersensitivity Reactions). Treating healthcare professionals must ensure that the patient is aware of the signs of hypersensitivity and the risk of anaphylaxis, and is capable of seeking assistance should early features of a serious hypersensitivity reaction occur.

2.6. Proposed changes to the product documentation

The only changes to the approved PI for Actemra relate to the proposed extended indication for GCA. No changes are proposed for the other parts of the approved PI.

3. Background

3.1. Information on the condition being treated

GCA is a chronic systemic vasculitis affecting large and medium sized arteries. Two categories of GCA have been distinguished: (i) cranial GCA, involving the extracranial branches of the carotid arteries; and (ii) large vessel GCA, involving the aorta and its primary branches (Weyand, 2003). Cranial GCA is considered the most typical presentation, consisting of a broad spectrum of clinical and laboratory abnormalities that are attributable to ischemia on one hand and systemic inflammation on the other. Common ischemic complications include severe headache, scalp tenderness and jaw claudication. The most feared ischemic complication is vision loss. Permanent vision loss affects approximately 15% to 20% of patients. Once vision loss is established, it is almost always permanent, but it can be prevented by early intervention (Borchers, 2012).

Large vessel GCA, which affects the aorta and its primary branches, particularly the subclavian, axillary and proximal brachial arteries, typically presents as vascular insufficiency to an extremity, for example, arm claudication or decreased/absent peripheral pulses (Brack, 1999). Large vessel GCA can lead to aortic aneurysms, aortic dissection (Warrington, 2014) and coronary arteritis (Butler, 2010).

The American College of Rheumatology (ACR) developed classification criteria for GCA based upon clinical, laboratory and histopathologic findings. The classification criteria were developed originally for the purpose of distinguishing GCA from other vasculitides (Hunder et al. 1990). GCA primarily affects adults who are 50 years of age or older and the risk for GCA increases with advancing age. The highest rates are observed in individuals between 70 and 79 years of age (Gonzàlez-Gay et al. 2009; Petri et al. 2014). GCA incidence peaks from age 70 to 79 in women and ≥ 80 years in men.

There is a significant increase in both incidence and prevalence with increasingly northerly latitudes with the highest incidence rates reported in Scandinavia and the United Kingdom at 20 to 30 cases per 100,000 people aged 50 years or older. By contrast, studies from southern Europe have consistently reported lower incidence rates at 7 to 10 cases per 100,000 people aged 50 years or older (Gonzàlez-Gay, 2009; Watts and Scott 2014). In the United States, GCA is most common in Caucasians of Scandinavian descent and is rare among African Americans

(Gonzàlez-Gay, 2009). In Olmsted County, Minnesota, US, home of many Scandinavian immigrants, the annual incidence is 19.8 to 22.9 cases per 100,000 people aged 50 years or older (Chandran, 2015). GCA appears to be rare in Asian populations with a reported prevalence of 1.5 cases per 100,000 people in Japan (Kobayashi et al. 2003). It is unclear as to whether these changes reflect the different genetic backgrounds of the populations and/or additional environmental factors.

3.2. Current treatment options

GCA represents a medical emergency, requiring prompt diagnosis and initiation of treatment to prevent sudden vision loss and other ischemic complications in patients with GCA (Matteson et al. 2016). The recommendations for GCA treatment, developed by EULAR and the British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR), are based on the current evidence and glucocorticoids are the cornerstone of treatment for GCA (Borchers and Gershwin 2012; Mukhtyar, 2009; Dasgupta, 2010).

Oral glucocorticoids (usually prednisone/ prednisolone) are initiated at a dose of 40 to 60 mg/day if a diagnosis of GCA is strongly suspected or confirmed by biopsy or imaging (Mukhtyar, 2009). Patients with complicated GCA, for example those with evolving vision loss or history of amaurosis fugax;[1] are often treated with IV methylprednisolone (500 mg to 1 g) daily for 3 days (Mazlumzadeh et al. 2006). Once the clinical signs and symptoms of GCA have subsided, typically after 2 to 4 weeks, the glucocorticoid dose is gradually tapered. The decision to reduce glucocorticoids is based on the regular assessment of clinical signs and symptoms and evaluation of the ESR or CRP levels.

Although some patients can discontinue glucocorticoids after 1 to 2 years of treatment, up to 2 thirds of patients experience disease relapses upon tapering or after complete withdrawal of glucocorticoids (Martinez-Lado et al. 2011; Andersson et al. 1986; Proven et al. 2003; Alba et al. 2014). Recurrence of disease after complete withdrawal of glucocorticoids occurs in more than 3 quarters of patients and is most often seen in the first year following completion of treatment (Hoffman et al. 2002; Hoffman et al. 2007). In some patients with cranial GCA, the disease takes a relapsing chronic course requiring indefinite treatment with glucocorticoids (Borchers and Gershwin 2012). Late vascular complications several years after a GCA diagnosis suggest that glucocorticoids doses sufficient to abate the signs and symptoms of cranial GCA may be inadequate to suppress or prevent vascular lesions in the large arteries (Nuenninghoff et al. 2003a; Borchers and Gershwin 2012).

Although glucocorticoids are highly effective at inducing remission in most GCA patients, they are associated with a high toxicity burden, with 86% of patients experiencing glucocorticoid related AEs after 10 years of follow up, including bone fractures, avascular necrosis of the hip, diabetes mellitus, infections, gastrointestinal bleeding, cataracts and hypertension (Nesher et al. 1994; Proven et al. 2003; Petri et al. 2014; Broder et al. 2016). In a 15 year study of patients with GCA, 58% of patients had at least one serious glucocorticoid related adverse effect during their course of treatment (Mukhtyar et al. 2009). Treatment with high dose glucocorticoids, especially in an elderly population, who commonly have multiple pre-existing comorbidities such as diabetes, hypertension and osteoporosis, carries serious risks (Weyand and Goronzy 2014). Moreover, cases of sudden death from high dose IV glucocorticoids have been reported (Gonzàlez-Gay et al. 2009; Mazlumzadeh et al. 2006).

Given the seriousness of glucocorticoid related AEs, considerable efforts should be made to minimise the duration of treatment and the cumulative glucocorticoid dose. Other immunosuppressive drugs have been considered as alternatives to glucocorticoids (or to reduce the need for glucocorticoids), with limited information or evidence of success. However, no

[1] Painless temporary loss of vision in one or both eyes.

agents capable of maintaining disease remission once glucocorticoid therapy has been discontinued have been approved.

While glucocorticoids have established themselves as standard of care, there are currently no treatments approved specifically for the treatment of GCA. The Mayo Clinic, EULAR and BSR/BHPR guidelines recommend considering the immunosuppressive agent methotrexate as adjunctive therapy (Warrington and Matteson 2007; Mukhtyar, 2009; Dasgupta, 2010). However, the available evidence for methotrexate in the management of GCA is limited and trials using methotrexate have yielded equivocal results (Jover, 2001; Spiera, 2001, Hoffman, 2002). A meta-analysis of individual patient data from these randomised controlled trials demonstrated a modest reduction in relapse and glucocorticoid exposure in the methotrexate treated groups (Mahr, 2007). However, a further meta-analysis of the same trials of methotrexate concluded there was no significant benefit (Yates, 2014). Open label studies have explored the effects of cyclosporine A, leflunomide, mycophenolate mofetil, or cyclophosphamide in the treatment of GCA but the patient numbers were too small to draw firm conclusions (Schaufelberger, 1998; Adizie, 2012; Sciascia, 2012; Quartuccio, 2012). Randomised clinical trials of anti-TNFi agents, including infliximab, adalimumab and etanercept, have shown no efficacy in GCA (Hoffman, 2007; Martinez-Taboada, 2008; Seror, 2014). A recent Phase II, randomised, double blind, placebo controlled, and withdrawal design trial of the CTLA-4 inhibitor abatacept has shown some evidence of efficacy in the treatment of GCA in 49 patients (Langford, 2015). However, the difference in treatment response between active and control arms was not compelling and would require further substantiation in the setting of a larger, more rigorous randomised clinical trial.

3.3. Clinical rationale

Elevated tissue and serum levels of IL-6 have been reported in the pathogenesis of GCA and correlate with disease activity. The pro-inflammatory, multifunctional cytokine IL-6 is produced by a variety of cell types, including T cells, B cells, monocytes, fibroblasts, keratinocytes and synovial and endothelial cells. IL-6 has been shown to be involved in diverse physiological processes, such as T cell activation, B cell differentiation, induction of immunoglobulin secretion, acute phase protein production, stimulation of hematopoietic precursor cell growth and differentiation, osteoclast differentiation from precursor cells, proliferation of hepatic, dermal and neural cells, and bone and lipid metabolism (Dayer and Choy 2010). It exerts its effects through the IL-6 receptor (IL-6R), which is present both in soluble and in membrane expressed forms. Its potential in the treatment of GCA stems from the putative role of IL-6 as a key cytokine in inflammation.

Tocilizumab is a recombinant humanised, anti-human monoclonal antibody of the IgG1 subclass. The molecule targets the soluble and membrane bound forms of the IL-6 receptor (sIL-6R and mIL-6R), adhering to the IL-6 binding site of these receptors and inhibiting IL-6 signalling in a competitive manner.

Following a compelling case study in 2010[2], a number of additional case studies reporting a therapeutic benefit of TCZ in 31 GCA patients were published; 29 patients received 8 mg/kg intravenously (IV) every 4 weeks (in some cases the starting dose was 8 mg/kg every 2 weeks)

[2] The patient was a [information redacted] year-old man who had been treated for 8 months with high doses of glucocorticoids that had never controlled his disease. He then presented abruptly with an aortic arch aneurysm and dissection, necessitating preparation for urgent surgery. In a desperate attempt to bring his aortic inflammation under control and facilitate surgery, the patient was treated with intravenous TCZ (8 mg/kg). Within 36 hours, a dramatic effect on the patient's sense of well-being was observed, accompanied by consistent declines in his acute phase reactants, even as his daily prednisone dose was tapered from 60 mg/day to 7.5 mg/day in preparation for surgery. The patient underwent a successful 13-hour aortic surgery procedure. Six years after this hospitalisation, he remains in complete remission from his GCA, continuing to receive TCZ without any glucocorticoid treatment at all over that period of time.

and 2 patients received 4 mg/kg IV every 4 weeks. Positive treatment effects of TCZ in GCA were reported, showing consistent achievement of remission, low risk of flares during treatment, rapid glucocorticoid taper to low dose or complete withdrawal and good tolerability of TCZ (Seitz et al. 2011; Christidis et al. 2011; Beyer et al. 2011; Unizony et al. 2012; Salvarani et al. 2012). Based on these observations, in 2012 the sponsor initiated a clinical development program based on a Phase III randomised, double blind, placebo controlled superiority study to evaluate SC TCZ in GCA. About the same time, a Phase II single centre, investigator initiated sponsor supported trial was begun to study the IV formulation of TCZ in GCA patients; that study was unblinded prior to the completion of Part 1 of Study WA28119 (Villiger et al. 2016).

Thus, inhibition of the biological activity of IL-6 by TCZ represents a promising new approach for the treatment of GCA.

3.4. Formulation

3.4.1. Formulation development

No new information is provided regarding formulation development.

3.4.2. Excipients

Actemra concentrated solution for intravenous (IV) infusion contains the following excipients; polysorbate 80, sucrose, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate dihydrate and water for injections.

Actemra solution for subcutaneous (SC) injection contains the following excipients histidine, histidine hydrochloride, polysorbate 80, arginine, arginine hydrochloride, methionine and water for injections.

3.5. Guidance

As there were no formal guidelines from any regulatory agencies about the requirements to obtain approval for an indication to treat GCA, the sponsor engaged in dialogues with Health Authorities in the USA and Europe to discuss the details of the development program for TCZ in GCA.

Pre-submission meetings or other pre-submission discussions with the TGA concerning this application were not held.

3.6. Evaluator's commentary on the background information

The stated clinical rationale is valid and acceptable.

4. Contents of the clinical dossier

4.1. Scope of the clinical dossier

The dossier documented a development program of pharmacology, dose finding, pivotal and other clinical trials relating to the proposed extension of indications.

- The PK and PD of TCZ in combination with a 26 week prednisone taper regimen in patients with GCA in the Phase III, multicentre, randomised, double blind placebo controlled Study WA28119.

- A population PK/PD analysis (PopPK), Study PopPK WA28119, in which a model was generated to explain TCZ concentration data collected over 52 weeks and included a tertile and graphical analysis of the exposure-response relationship of selected PD, efficacy and safety parameters collected over this period.
- Pivotal efficacy/safety study: Phase III, multicentre, randomised, placebo controlled, double blind, parallel group superiority Study WA28119 (GiACTA) in patients with GCA designed to evaluate the safety and efficacy of TCZ for the treatment of GCA.
- Other efficacy/safety studies:
  - Study ML25676 (Villiger, 2016) data from this study using IV TCZ was included to provide supportive evidence of efficacy/ safety of TCZ in treatment of GCA. However, the original CSR was not provided for evaluation.
  - Real world evidence report: Analysis of oral glucocorticoid use over time, expected incidence rates of safety events of interest and risk associated with cumulative use of oral glucocorticoids in giant cell arteritis patients in MarketScan.
- Literature references.

4.2. Paediatric data

The proposed extended indication of Actemra is for treatment of GCA in adults only.

4.3. Good clinical practice

The pivotal Study WA28119 included in this application was conducted in accordance with the principles of the 'Declaration of Helsinki', the U.S. Food and Drug Administration regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and applicable local, state and country laws. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved all studies.

4.4. Evaluator's commentary on the clinical dossier

The submission was well presented.

5. Pharmacokinetics

5.1. Studies providing pharmacokinetic information

The following table summarises the submitted pharmacokinetic (PK) studies.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in special populations	Target population § Multidose	WA28119	PK and PD of TCZ in combination with a 26 week prednisone taper regimen in patients with GCA.
Population PK analyses	Target population	PopPK WA28119	Development of a popPK model using TCZ concentration data collected over 52 weeks from patients with GCA and which included a tertile and graphical analysis of the exposure-response relationship of selected PD, efficacy and safety parameters

* Indicates the primary PK aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

5.2. Summary of pharmacokinetics

5.2.1. Methods of PK Analysis

The concentration of TCZ was determined in human serum using a validated ELISA method. The calibration range was 1.25 ng/mL to 160 ng/mL (concentration in assay) corresponding to 50.0 ng/mL to 6400 ng/mL of TCZ in native serum. The lower limit of quantification (LLOQ) was 100 ng/mL (concentration in native serum) using 250 µL of 40 fold diluted serum sample aliquots.

5.2.2. Physicochemical characteristics of the active substance

Tocilizumab is a recombinant humanised anti-human monoclonal antibody of the Immunoglobulin G (IgG) subclass directed against the interleukin–6 (IL-6) receptor to inhibit the function of IL-6.

5.2.3. Pharmacokinetics in healthy subjects

Comment: No new studies contained in the present submission examined the PKs of Actemra in healthy subjects. Therefore, the following discussion pertains to the PKs of Actemra in patients with GCA only.

5.2.4. Absorption

5.2.4.1. *Sites and mechanism of absorption*

Actemra is to be administered via SC injection and the recommended dose for adult patients with GCA is 162 mg given once every week (QW). PopPK analysis (Study PopPK WA28119,) indicated that TCZ had first order absorption and an estimated absorption rate constant (ka) in patients with GCA of 0.193 day^{-1} (Table 2). In GCA patients at steady state, the analysis predicted that following a 162 mg SC dose of TCZ QW, the median Tmax occurred approximately 3 days following dosing (Table 3).

Table 2: Study PopPK WA28119 parameter estimates of the final Model 107

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}	Ω(1,1)	0.0561	26.7	0.0267 - 0.0854	CV=23.7	27.1
ω^2_{V2}	Ω(2,2)	0.0822	18.6	0.0522 - 0.112	CV=28.7	10.0
ω^2_{V3}	Ω(3,3)	0.227	63.5	0 - 0.508	CV=47.6	48.9
ω^2_{ka}	Ω(4,4)	0.174	22.3	0.0982 - 0.251	CV=41.8	25.6
ω^2_{EPS}	Ω(5,5)	0.129	16.7	0.0871 - 0.172	CV=36.0	1.9
σ^2	Σ(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

Table 3: Study PopPK WA28119 summary of predicted individual steady state exposure parameters, Model 107

Treatment Arm	N	AUCτ (µg/mL*day)	C_{mean} (µg/mL)	C_{max} (µg/mL)	T_{max} (day)	C_{trough} (µg/mL)
		Mean (SD)				
SC 162 mg QW	100	499.2 (210.4)	71.3 (30.1)	73.0 (30.4)	3 (0.1)	68.1 (29.5)
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]				
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]
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]

5.2.5. Bioavailability

5.2.5.1. *Absolute bioavailability*

The bioavailability of the SC formulation of Actemra has been previously reported to be 0.8.

5.2.5.2. *Bioavailability during multiple dosing*

Study WA28119 was a Phase III, multicentre, randomised, double blind placebo controlled study, which assessed the PKs and PDs of TCZ following 162 mg doses of SC TCZ QW or every other week (Q2W) in combination with a 26 week prednisone taper regimen in patients with GCA. Serum TCZ concentration data were collected from 147 of the 250 patients treated and represented the results from 99 patients in the TCZ QW treatment group and 48 patients in the TCZ Q2W group. Additional PK samples were taken from 8 patients who agreed to take part in a substudy, which assessed the PKs of TCZ in GCA patients.

The mean (± SD) TCZ serum concentration at Week 52 following the recommended dose was 67.93 ± 34.40 µg/mL. The mean ± SD values of pre-dose TCZ concentrations at Week 52 for responders and non-responders were 69.18 ± 35.00 µg/mL and 64.89 ± 33.51 µg/mL, respectively.

The PopPK analysis provided estimates of the mean steady state C_{mean}, C_{max} and C_{trough} values following 26 weeks of QW dosing in patients with GCA of 66.4 µg/mL, 68.1 µg/mL and 63.3 µg/mL, respectively.

Approximately 90% of the steady state exposure levels were reached by week 17 following QW dosing and the accumulation ratios for AUCτ, C_{max} and C_{trough} were estimated to be 10.9, 8.9 and 9.6, respectively.

5.2.5.3. *Effect of administration timing*

As stated in the preceding section of this report, Study WA28119 also examined the effect of Q2W dosing on TCZ serum concentrations in patients with GCA. At Week 52 following Q2W dosing, mean exposure to TCZ was approximately 5.5 fold lower than following QW dosing as the mean TCZ concentrations detected in GCA patients were 67.93 ± 34.40 µg/mL and 12.22 ± 10.02 µg/mL for the TCZ QW and TCZ Q2W groups, respectively. Similarly, the TCZ levels in responders and non-responders were also considerably lower following Q2W dosing than QW dosing. For instance in patients classified as responders, mean TCZ concentration values at 52 weeks were 69.18 ± 35.00 µg/mL in the QW group and 13.26 ± 10.43 µg/mL in the Q2W group; in patients classified as non-responders, mean TCZ concentration values at 52 weeks were 64.89 ± 33.51 µg/mL in the QW group and 8.95 ± 8.38 µg/mL in the Q2W group.

Results from the PK substudy supported these findings and indicated that although TCZ concentrations were comparable in the 2 dose groups after the first dose and TCZ concentrations were higher in both dose groups at Week 16 compared to the first dose, exposures in the TCZ QW group were approximately 4 fold higher than in the TCZ Q2W group.

Unsurprisingly, as the dataset of the PopPK analysis comprised of the results of Study WA28119, the PopPK study also predicted that TCZ exposure was lower following Q2W dosing. For instance, the estimated C_{mean} values following QW and Q2W dosing were 66.4 and 14.7 µg/mL, respectively; the mean C_{max} values were 68.2 and 18.0 µg/mL, respectively, and the mean C_{trough} values were 63.3 and 9.5 µg/mL, respectively.

Similarly the accumulation ratios for AUCτ, C_{max} and C_{trough} were also estimated to be lower following Q2W dosing with predicted values of 2.8, 2.3 and 5.6, respectively.

5.2.6. Distribution

The popPK study provided estimates for TCZ of the central volume of distribution and the peripheral volume of distribution in patients with GCA of 4.09 L and 3.37 L.

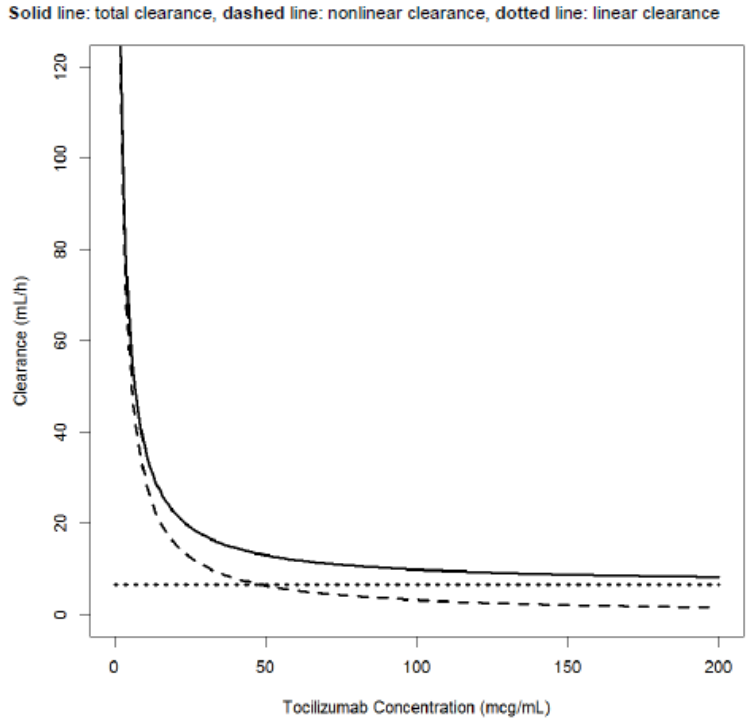
5.2.7. Metabolism

The metabolism of TCZ was not discussed as part of the present submission, nor was it described in the proposed PI. However, given that TCZ is a monoclonal IgG antibody, one would assume that the majority of the elimination occurs via intracellular catabolism.

5.2.8. Excretion

TCZ elimination comprises 2 components: linear and non-linear clearance. At very low concentrations (for example 2 µg/mL), TCZ elimination is almost entirely dependent upon non-linear clearance, which was approximately 18 fold higher than linear clearance. By contrast, at concentrations above 200 µg/mL, the influence of non-linear clearance becomes negligible (less than 20%) and total clearance is dominated by linear clearance, whereas, at TCZ concentrations of around 50 µg/mL the 2 components of total clearance contribute equally to TCZ elimination (Figure 1).

Figure 1: Study PopPK WA28119 dependence of total, linear and non-linear clearance on TCZ serum concentrations



Similarly, due to the interdependence between half-life ($t_{1/2}$) and elimination, the $t_{1/2}$ of TCZ is also concentration dependent and can only be calculated at a given serum concentration level. The effective half-life of TCZ at steady state was found to vary between 18.3 and 18.9 days for 162 mg SC QW regimen and between 4.2 and 7.9 days for 162 mg SC Q2W regimen. At high serum concentrations, when total clearance of TCZ is dominated by linear clearance, an effective half-life of approximately 32 days was derived from the population parameter estimates.

Following simulations of the changes in TCZ serum concentrations over time, steady state PK profiles over a 2 week interval, it was estimated that saturation of the non-linear elimination pathway was more pronounced at 162 mg QW SC regimen compared to Q2W, resulting in less variation of total clearance over the dosing interval.

5.2.9. Intra and inter individual variability of pharmacokinetics

The popPK analysis indicated that the inter-individual variance values for clearance, ka and the volume of distribution of the central (Vc) and peripheral compartments (Vp) were 0.056, 0.174,

0.082 and 0.227, respectively, and the variance on the residual error was 0.129 (Table 4). For further information regarding the popPK study please see below of this report.

Table 4: Study PopPK WA28119 parameter estimates of the final Model 107

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}	Ω(1,1)	0.0561	26.7	0.0267 - 0.0854	CV=23.7	27.1
ω^2_{V2}	Ω(2,2)	0.0822	18.6	0.0522 - 0.112	CV=28.7	10.0
ω^2_{V3}	Ω(3,3)	0.227	63.5	0 - 0.508	CV=47.6	48.9
ω^2_{ka}	Ω(4,4)	0.174	22.3	0.0982 - 0.251	CV=41.8	25.6
ω^2_{EPS}	Ω(5,5)	0.129	16.7	0.0871 - 0.172	CV=36.0	1.9
σ^2	Σ(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

5.2.10. Pharmacokinetics in the target population

Please see the preceding sections of this report.

5.2.11. Pharmacokinetics in special populations

5.2.11.1. *Pharmacokinetics in subjects with impaired hepatic function*

Not examined.

5.2.11.2. *Pharmacokinetics in subjects with impaired renal function*

Not examined.

5.2.11.3. *Pharmacokinetics according to age*

The PopPK analysis identified age as a significant covariate of ka and compared to a reference age of 50 years, patients with ages of 54 years and 84 years would have the value of ka decreased by 3.1 % or 20.5 %, respectively (Table 5).

Table 5: Predicted Covariate Effects

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.

5.2.11.4. *Pharmacokinetics related to genetic factors*

Not examined.

5.2.11.5. *Pharmacokinetics in other special population / with other population characteristic*

Please see the following section of this report.

5.3. Population pharmacokinetics

5.3.1. PopPK analysis

The popPK analysis was undertaken using a dataset that contained 1263 quantifiable serum samples from 149, primarily Caucasian, patients with GCA who were enrolled in Study WA28119. Previously, it was reported that the PKs of TCZ in 1759 RA patients were best described by a 2 compartment model with parallel linear and Michaelis-Menten elimination. For this model the covariates identified included: body weight on CL, inter-compartmental clearance (Q), Vc and Vp; HDL cholesterol on CL; serum albumin and total protein on Vc and Vp; creatinine clearance on Michaelis-Menten parameter Vmax; age on ka; and injection site on bioavailability (Fsc). These results were then used as a starting point for the current PopPK analysis in patients with GCA, which also identified that the model (Model 107) that best described the PK data was a 2 compartment model with parallel linear and Michaelis-Menten elimination (Table 4). For instance, simulated concentration-time profiles of 5000 patients for each dosing regimen (median values and 90% prediction intervals) and the simulated profiles for patients in the dataset based on their individual parameters were nearly identical (Figures 2 and 3).

Figure 2: Study PopPK WA28119 concentration-time course, population predictions for Model 107

Median (red) and 90% prediction intervals (blue) of the simulated concentration-time profiles following SC administration of 162 mg QW doses, and SC administration of 162 mg Q2W doses. For each dosing regimen concentrations were simulated for 5000 patients with the covariate values sampled with replacement from the analysis population. **Top row**: the full concentration-time course following the first and the last dose, and trough concentrations between these profiles. **Bottom row**: the full concentration-time course following the last dose of 48-week dosing.

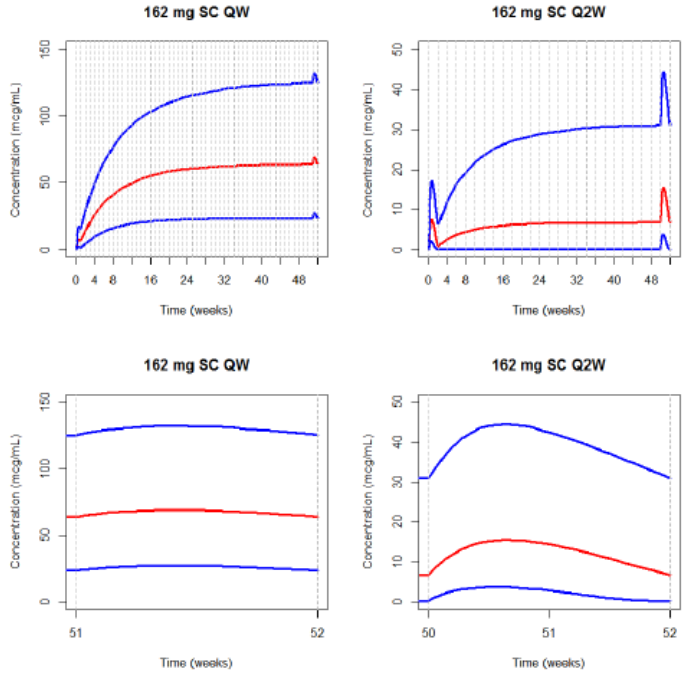
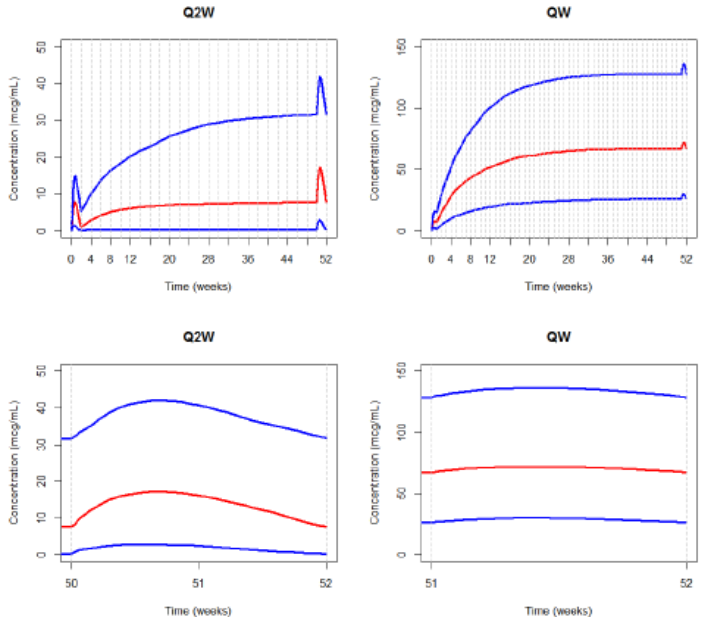


Figure 3: Study PopPK WA28119 concentration-time course, individual predictions for Model 107

Median (**red**) and 90% prediction intervals (**blue**) of simulated concentration-time profiles following SC administration of 162 mg QW doses and SC administration of 162 mg Q2W doses. Individual PK parameters of patients from the corresponding dosing groups and per protocol dosing were used for simulation. **Top row**: the full concentration-time course following the first and the last dose, and trough concentrations between these profiles. **Bottom row**: the full concentration-time course following the last dose of 48-week dosing.



The covariates included in the final model were: body weight on CL, Vc and Vp; age on ka and injection site (thigh) on bioavailability. The reference value for body weight was 70 kg and body weights of 48.6 kg and 102 kg resulted in a 34% decrease and 53.6% increase in CL values, respectively. As mentioned, body weight was also a covariate of Vc and Vp and compared to the reference weight of 70 kg, patients with a body weight of 48 kg had Vc and Vp decreased by 21.6%, whereas subjects with a body weight of 102 kg had Vc and Vp values increased by 28.5% (Table 5). Compared to a SC injection into the arm or abdomen, injection into the thigh resulted in an 11.5% increase in bioavailability in GCA patients, which was consistent with the results of initial RA analysis (11%) and was considered not to be clinically relevant by the sponsor.

5.4. Pharmacokinetic interactions

Not examined.

5.5. Evaluator's overall conclusions on pharmacokinetics

- TCZ is a recombinant humanised anti-human monoclonal antibody, which is directed against the IL-6. It is to be administered once weekly via SC injection.
- The estimated ka and Tmax of TCZ at steady state in patients with GCA is 0.193 day^{-1} and 3 days, respectively.
- The bioavailability of the SC formulation of Actemra has been previously reported to be 0.8.
- In patients with GCA administered 162 mg SC doses of TCZ QW for 52 weeks, the mean (± SD) TCZ serum concentration was 67.93 ± 34.40 µg/mL, whereas, the pre-dose TCZ concentrations in responders and non-responders were 69.18 ± 35.00 µg/mL and 64.89 ± 33.51 µg/mL, respectively.
- The proposed weekly dosing with TCZ for treatment of GCA appears to be justified as TCZ exposure was considerably higher (approximately 5.5 fold) following administration QW compared Q2W as the mean TCZ concentration detected in GCA patients following 24 weeks of QW dosing and Q2W dosing were 68.18 µg/mL and 12.46 µg/mL, respectively.
- The estimated central and the peripheral volume of distributions of TCZ in patients with GCA were 4.09 L and 3.37 L, respectively.
- TCZ elimination is comprised of linear and non-linear clearance and at TCZ serum concentrations of around 50 µg/mL the 2 components contribute equally to TCZ elimination. Therefore, the $t_{1/2}$ of TCZ is also concentration-dependent and the effective $t_{1/2}$ of TCZ at steady-state was found to vary between 18.3 and 18.9 days for 162 mg SC QW regimen
- The estimated inter-individual variance on clearance, ka, Vc and Vp were 0.056, 0.174, 0.082 and 0.227, respectively, and the variance on the residual error was 0.129.
- The TCZ serum concentration data in patients with GCA was best described by a 2 compartment model with parallel linear and Michaelis-Menten elimination. The covariates included in the final model were: body weight on CL, Vc and Vp; age on ka and injection site (thigh) on bioavailability.
- The PK aspects of the proposed PI are satisfactory.

6. Pharmacodynamics

6.1. Studies providing pharmacodynamic information

Both of the new studies included in the evaluation materials that contain PD results also contain PK data and therefore have been summarised in Table 1 of this report.

6.2. Summary of pharmacodynamics

6.2.1. Mechanism of action

The following statements regarding the mechanism of action are taken from the proposed PI version 161118D.

TCZ binds specifically to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a multi-functional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T cell activation, and induction of hepatic acute phase proteins and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including rheumatoid arthritis (RA).

6.2.2. Pharmacodynamic effects

The PD effects of TCZ in patients with GCA were characterised by assessing 2 markers for cytokine activity: soluble interleukin-6 receptor (sIL-6R) and IL-6 levels; as well as 2 inflammation markers: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

6.2.2.1. *Primary pharmacodynamic effects*

IL-6 and sIL-6

As described previously in this report, Study WA28119 was a Phase III, multi-centre, randomised, double blind placebo controlled study, which assessed the PKs and PDs of TCZ following 162 mg doses of SC TCZ QW or Q2W in combination with a 26 week prednisone taper regimen in patients with GCA. As a part of the PD assessment, sIL-6R levels were examined at various points during the TCZ treatment period. The results indicated that following the initiation of TCZ therapy, sIL-6R levels increased over the initial 16 Weeks of treatment, whereas, from Week 16 through to Week 52 sIL-6R levels were relatively stable. At Week 52, the sIL-6R levels (mean ± SD) were 29% higher in the TCZ QW group (600.53 ± 217.52 ng/mL) than in the TCZ Q2W group (464.30 ± 153.64 ng/mL).

Similarly, following the initial TCZ dose, IL-6 levels increased by approximately 14.3 fold over pre-dose levels; however by Week 52, the increase in IL-6 levels had diminished and levels were approximately 7.5 fold higher than baseline. At Week 52, IL-6 levels were 25% higher in the TCZ QW treatment group than in TCZ Q2W group. In contrast to the TCZ treated patients, sIL-6R and IL-6 levels in placebo treated subjects were unchanged over the 52 week study period.

CRP and ESR

Baseline levels of the inflammatory markers, CRP and ESR were close to the high normal range of healthy humans in all patients. However, following the initiation of treatment with TCZ (both QW and Q2W), median CRP and ESR values decreased rapidly and remained low throughout the remainder of the study. By contrast, in subjects administered placebo, the mean CRP and ESR levels remained unchanged from their baseline levels throughout the 52 week treatment period.

Time to first flare

A total of 250 patients (149 and 101 from the TCZ and placebo treatment arms, respectively) were included in the first-flare analysis. As more than 90% of the GCA patients who experienced a flare had their first flare 8 weeks or later after starting TCZ treatment, the individual predicted average concentration up to Week 8 from treatment start (Cave8) was selected as an early exposure parameter to assess its ability to predict time to flare (Table 6).

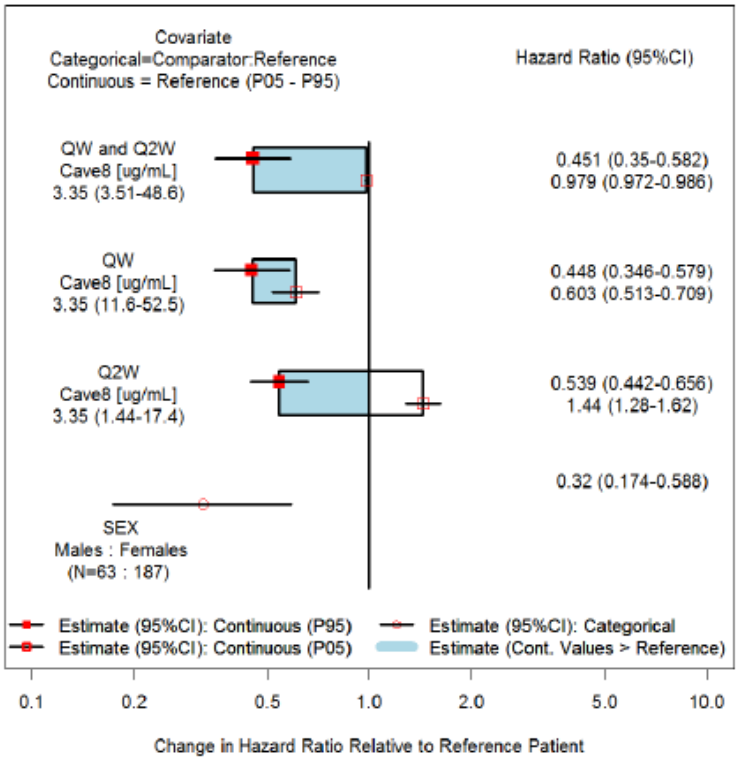
Table 6: Study PopPK WA28119 tertiles of C_{ave8}

Exposure Tertile		N	C_{ave8} Range (µg/mL)
1	Low	50	0.50 - 14.0
2	Middle	49	14.3 - 29.1
3	High	50	29.1 - 69.9

The model predicted that the risk of flare in males was around 3 times lower than in females (HR = 0.320) (see Figure 4). For the patients that received TCZ, where the 95th percentile of Cave8 was 48.6 µg/mL, the first flare hazard was reduced by 55% (HR = 0.451). Exposure at the 5th percentile was approximately equal to EC50 (and, thus the hazard did not change).

In patients administered TCZ QW, the risk of flare was reduced by 40% (HR = 0.603) for patients at the 5th exposure percentile (Cave8 = 11.6 µg/mL) and 55% (HR = 0.448) for patients at the 95th percentile (Cave8 = 52.5 µg/mL). By contrast, for the Q2W TCZ treatment arm, risk of flare was increased by 44% (HR = 1.44) for patients at 5th percentile (Cave8 = 1.44 µg/mL), whereas, at the 95th percentile of exposure (Cave8 = 17.4 µg/mL) flare risk was reduced by 46%.

Figure 4: Study PopPK WA28119 TTF analysis: covariate effects on the hazard ratio for the final CPH Model



6.2.2.2. *Secondary pharmacodynamic effects*

Immunogenicity

As part of Study WA28119, blood samples were collected from 92.2% to 98.0% of the Safety Population at Baseline, Weeks 8, 24 and 36 and at the completion of the blinded phase (Week 52) for investigating the existence of anti-TCZ antibodies in serum using a validated ELISA method[3]. The results indicated that overall the proportion of patients that developed treatment-induced ADAs was low, as only 1 (1.1%) patient tested positive in the TCZ QW-treatment arm and 3 (6.5%) patients tested positive in the TCZ Q2W arm (Table 7). No patients experienced anaphylaxis, serious / clinically significant hypersensitivity reactions, ISRs, or withdrew due to a lack of efficacy. All 4 patients developed ADAs with neutralising potential but no patients had ADAs of the IgE isotype.

Two patients from the placebo groups (one from each of the PBO + 26 week and PBO + 52 week groups) were also positive for treatment-induced ADAs, but as these patients never received TCZ they were considered to be false positives. In all 6 patients that tested positive for treatment-induced ADAs, ADA positive titres were transient and in the TCZ population only occurred at study weeks 24 and 36.

In a group of TCZ treated patients that demonstrated low TCZ serum concentrations (that is, < 10 µg/mL, n = 109) or TCZ levels below the limit of quantitation (BLQ, n = 21), 3 patients, all administered TCZ Q2W, developed treatment induced ADAs (Table 8).

ADAs at Baseline

Taking into account a 5% false positive rate in order to minimise the potential for false negative results, 13 (5.3%) out of 245 patients who provided baseline samples were positive for baseline ADAs. Of these, 6 patients (1 patient from each of PBO + 52 week and TCZ QW groups and 4 patients from the TCZ Q2W group) were also positive for the confirmation assay at Baseline (Table 7).

Table 7: Study WA28119 Summary of Patients Who Developed Treatment-Induced ADA up to Week 52 (Safety 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)
Baseline				
No. of Baseline evaluable patients (%)	50 (100.0)	49 (96.1)	99 (99.0)	47 (95.9)
No. of patients with screening assay +	0	2 (3.9)	6 (6.0)	5 (10.2)
No. of patients with confirmation assay +	0	1 (2.0)	1 (1.0)	4 (8.2)
Post-Baseline				
No. of evaluable patients	49 (98.0)	47 (92.2)	95 (95.0)	46 (93.9)
No. of patients with treatment-induced ADA	1 (2.0)	1 (2.1)	1 (1.1)	3 (6.5)
Post-Baseline ADA Characterization				
No. of patients with treatment-induced ADA of neutralizing potential	0	0	1 (1.1)	3 (6.5)
No. of patients with treatment-induced ADA of IgE isotype	0	0	0	0

[3] Bert Klunder. VR-0689. Validation of an immunoassay method for the determination of anti-Tocilizumab (TCZ) antibodies in human serum samples - screening and confirmatory assay -, issued 29 June 2010

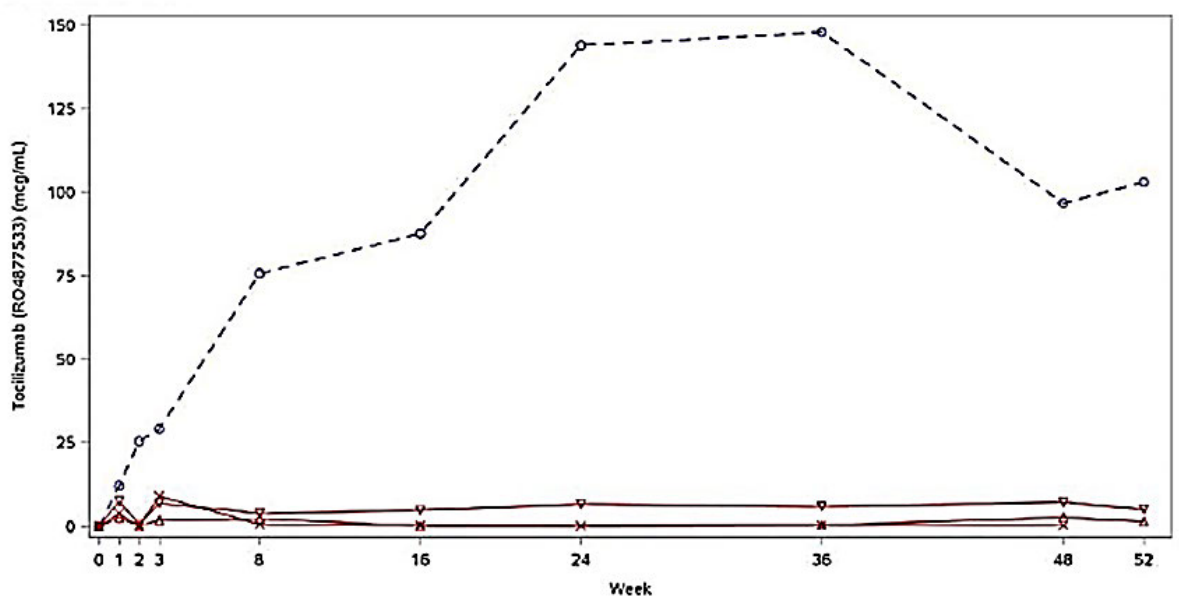
Table 8: Study WA28119 ADA development in patients with TCZ-free or TCZ-low post-Baseline samples up to Week 52 (Safety population)

Category	TCZ QW + 26 week Prednisone taper (N=100)	TCZ Q2W + 26 week Prednisone taper (N=49)
TCZ-Free (BLQ)		
Total no. of patients with at least one sample	6	16
No. of evaluable patients	6	15
No. of patients with treatment-induced ADA (%)	0	1 (6.7)
TCZ-low (<10 µg/mL)		
Total no. of patients with at least one sample	67	47
No. of evaluable patients	65	45
No. of patients with treatment-induced ADA	0	2 (4.4)

Effects of Treatment-Induced ADA on PKs

In 2 patients, who were both receiving TCZ Q2W and were positive for treatment induced ADAs, TCZ concentrations appeared to show a transient decrease at the Week 24 visit when ADAs were detected; but there was no sustained decrease at subsequent visits where ADA measures also became negative (Figure 5).

Figure 5: Study WA28119 TCZ plasma concentrations over time in patients with treatment-induced ADAs



Solid red line indicates TCZ Q2W group (n=3) and dashed blue indicates the TCZ QW group (n=1) in individual patients.

6.2.3. Time course of pharmacodynamic effects

6.2.3.1. *Relationships between TCZ exposure and time-course of PD effects*

Graphical analyses were undertaken as part of the popPK analysis using the data obtained from patients with GCA in Study WA28119.[4]

The results indicated that in the group administered placebo, CRP increased from Baseline, whereas, it declined in patients treated with TCZ. In addition in these patients, CRP values declined to nearly zero and remained at very low levels during the whole observation period. By contrast, ESR levels on the whole remained unchanged in the patients receiving placebo (25th percentile and median slightly increased), whereas, ESR declined strongly following administration of TCZ and it remained at low levels for most patients for the entire observation period. Levels were slightly lower in the 2 upper tertiles of exposure compared to the lowest tertile of exposure. For both, CRP and ESR, the observed inter-individual variability decreased with increasing exposure.

IL-6 concentrations in the placebo group remained constant (around 10 pg/mL) during treatment, whereas in groups administered TCZ, IL-6 increased to about 70 pg/mL 2-4 weeks following the initiation of treatment and then slowly declined to about 50 pg/mL. There were no meaningful differences in IL-6 levels between the 3 TCZ exposure tertiles.

Following the administration of placebo sIL-6R concentrations remained constant, whereas, in the groups administered TCZ, sIL-6R slowly increased and reached maximum levels 2-3 months after treatment initiation. Furthermore, at the end of treatment, sIL-6R levels were increased as exposure to TCZ increased.

6.2.3.2. *Relationships between TCZ exposure and time course of efficacy measures*

The score for the patient's global assessment, rated on a visual analog scale, (PGA VAS) decreased in all of the treatment groups, including placebo and there were no differences in the magnitude of decrease between the 3 TCZ exposure tertiles. The results of the Short Form-36 (SF-36), a 36 item questionnaire, which measures the quality of the patient's life, indicated that physical component scores (PCS) increased slightly in the TCZ exposure tertiles, whereas, it was unchanged in the placebo tertiles. The effect was similar in all TCZ exposure groups at the end of treatment, but appeared earlier in the 2 upper tertiles of exposure compared to the lowest exposure tertile. By contrast, the mental component SF-36 score increased slightly in all groups, including the placebo group and there were no differences in the magnitude of the effect between the groups.

6.2.4. Relationship between drug concentration and pharmacodynamic effects

The relationship of systemic TCZ exposure to PD and efficacy was investigated by tertile and graphical analysis on the data collected from Study WA28119 as part of the popPK analysis.

6.2.4.1. *Relationships between TCZ exposure and efficacy parameters*

There were no differences in the distributions of $C_{trough,52}$ for patients in the active TCZ treatment arms who achieved and did not achieve sustained remission up to Week 52 (REMI52). The logistic regression also did not indicate a significant relationship between exposure and probability of REMI52 (Table 9). The percentage of patients with REMI52 was much lower in the placebo group and was slightly higher in the highest exposure group relative to the lowest and middle exposure groups, but the confidence intervals were wide and overlapping (Table 10).

[4] The relationship of systemic TCZ exposure to PD was investigated graphically using TCZ $C_{trough52}$ grouped into tertiles as an exposure surrogate

Table 9: Study PopPK WA28119 summary of logistic regression models for sustained remission up to Week 52

Endpoint	Exposure Scale	N	Intercept	Slope	p-value
Remission at Week 52	Original	149	0.00445	0.00403	0.378
	Log	149	-0.0786	0.0844	0.456

Table 10: Study PopPK WA28119 frequency of sustained remission up to Week 52 by exposure

Exposure (tertile of $C_{trough52}$)	Total N	Patients In Remission	
		N	% (95% CI)
Placebo	101	16	15.8 (9.6 - 24.8)
Low (1st tertile)	50	25	50.0 (36.6 - 63.4)
Middle (2nd tertile)	49	26	53.1 (38.4 - 67.2)
High (3rd tertile)	50	31	62.0 (47.2 - 75.0)

During the treatment period, the fraction of patients in remission was lowest in the group that received placebo, whereas, remission levels were highest and similar in the 2 groups who experienced the highest exposure to TCZ. In the lowest exposure group, this fraction was similar to the placebo arm during the first 3-4 months of treatment, but reached the remission rate of the other 2 exposure groups by the end of the treatment period.

By contrast, the annualised relapse rate up to Week 52 (ARR52) was highest in the group receiving placebo, whereas, it was much lower in the active TCZ groups, with a slight numerical (but not statistically significant) decrease with increasing exposure.

The cumulative corticosteroid dose (CCD) was also highest in the placebo group, whereas, there were no differences in median CCD for patients in the different groups administered TCZ; however, in patients with higher than median values, CCD were lower in the highest exposure category compared to low and middle exposure categories.

6.2.4.2. *Relationships between TCZ concentrations and occurrence of AEs*

Occurrence of SAEs, AEs of Infections and Infestations (II AEs), and gastrointestinal AEs (GI AEs) were not correlated with TCZ exposure: concentration-time profiles of patients with events were neither higher nor lower than the concentration-time profiles of patients without events in each of the TCZ treatment arms. The logistic regression models (Table 11) indicated that there were no significant relationships between probability of AEs of these types and exposure. 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.

Table 11: Study PopPK WA28119 summary of logistic regression models for AEs

Endpoint	Exposure Scale	N	Intercept	Slope	p-value
any SAE	Original	149	-1.59	-0.00344	0.596
	Log	149	-1.68	-0.0235	0.880
any Grade 3+ SAE	Original	149	-2.1	0.00224	0.742
	Log	149	-2.46	0.138	0.483
AE of Infections and Infestation	Original	149	0.863	0.00435	0.411
	Log	149	0.777	0.0898	0.469
Grade 3+ AE of Infections and Infestation	Original	149	-2.51	0.00145	0.860
	Log	149	-2.68	0.0737	0.741
AE of Gastrointestinal Disorders	Original	149	-0.89	0.00644	0.169
	Log	149	-0.955	0.116	0.350
Grade 3+ AE of Gastrointestinal Disorders	Original	149	-4.88	0.0104	0.573
	Log	149	-7.68	0.877	0.434

6.2.4.3. *Relationships between TCZ concentrations and safety outcomes*

Overall, AEs related to neutropaenia were uncommon, as no patients in the placebo group experienced neutropaenia, one (2%) was identified in the TCZ Q2W group and 4 patients with neutropaenia (4%) were identified in the QW group. Among the 4 patients with neutropaenia in the QW arm, 2 patients had Grade 3+ neutropaenia. Occurrence of neutropaenia was not correlated with TCZ exposure: concentration-time profiles of patients with events were neither higher nor lower than concentration-time profiles of patients without them. There was only 1 patient with thrombocytopaenia (in the Q2W group), the same patient that had neutropaenia in this dosing group. Concentrations of this patient were similar to concentrations of many other patients in this dosing group.

White blood cell counts declined in all of the treatment groups, including placebo, with the largest (and a similar) decline identified in the 2 upper tertiles of TCZ exposure, a slightly lower decline in the lowest tertile of exposure and the smallest decline in the placebo group.

Similar patterns were observed for neutrophil counts. Platelet counts did not decrease over the course of treatment in the placebo group and declined slightly in all TCZ treatment groups, where the effect was similar in all exposure categories.

No changes over time in any of the groups were noticeable for total bilirubin, ALT, AST, total protein and total cholesterol.

Concentrations of serum albumin did not change in the placebo group and slightly increased over time in the active treatment arms. The increases did not depend on TCZ exposure and for all exposure groups albumin levels stayed below the upper normal level. LDL cholesterol levels were unaffected by placebo, whereas, they were mildly increased in the TCZ treatment groups; however, the increases did not appear to be dependent on TCZ exposure.

6.2.5. Genetic, gender and age related differences in pharmacodynamic response

Not examined.

6.2.6. Pharmacodynamic interactions

Not examined.

6.3. Evaluator's overall conclusions on pharmacodynamics

- TCZ binds specifically to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit sIL-6R and mIL-6R-mediated signalling.

- Following the initiation of TCZ therapy in patients with GCA, sIL-6R levels increased over the initial 16 Weeks of treatment, whereas, from Week 16 through to Week 52 sIL-6R levels were relatively stable. At Week 52, the sIL-6R levels were 29% higher in the TCZ QW group than in the TCZ Q2W group.
- IL-6 levels increased by approximately 14.3 fold over pre-dose levels following the initial TCZ dose; however by Week 52 the increase in IL-6 levels had diminished and levels were approximately 7.5 fold higher than baseline. At Week 52, IL-6 levels were 25% higher in the TCZ QW treatment group than in TCZ Q2W group. Following the initiation of treatment with TCZ, median CRP and ESR values decreased rapidly and remained low throughout the remainder of the study. In contrast to the TCZ treated patients, sIL-6R, IL-6, CRP and ESR values were unchanged in subjects administered placebo.
- Analysis of the safety population for the development of anti-TCZ antibodies indicated that the incidence of treatment-induced ADAs was low: 1 (1.1%) and 3 (6.5%) patients for the TCZ QW and TCZ Q2W treatment arms, respectively. No patients experienced anaphylaxis, serious / clinically significant hypersensitivity reactions, ISRs, or withdrew due to a lack of efficacy. All 4 patients developed ADAs with neutralising potential but no patients had ADAs of the IgE isotype.
- Three TCZ treated patients, all in the TCZ Q2W treatment arm, who demonstrated low or undetectable serum levels of TCZ developed treatment induced ADAs.
- Thirteen (5.3%) out of 245 patients who provided baseline samples were positive for baseline ADAs.
- Two patients from the placebo groups were also positive for treatment-induced ADAs.
- In all 6 patients that tested positive for either TCZ- or placebo-treatment-induced ADAs, positive ADA titres were transient and in the TCZ population only occurred at study weeks 24 and 36.
- In 2 patients, who were both receiving TCZ Q2W and were positive for treatment induced ADAs, TCZ concentrations appeared to show a transient decrease at the Week 24 visit when ADAs were detected; but there was no sustained decrease at subsequent visits where ADA measures also became negative.
- Modelling of the time to first flare estimated that the risk of flare in males was ~3 times lower than in females and in patients receiving TCZ, where the 95th percentile of Cave8 was 48.6 µg/mL, the first flare hazard was reduced by 55%.
- Overall, the risk of flare was diminished considerably at lower TCZ exposure levels following QW- than Q2W-dosing (approximately 84% at the 5^{th} exposure percentile), whereas, when higher TCZ exposure levels were achieved the difference between the risks of flare for the 2 dosing regimens was reduced.
- Graphical analyses undertaken as part of the PopPK study indicated that, in subjects administered TCZ, CRP and, ESR declined to and remained at low levels throughout the observation period, whereas, IL-6 levels increased (from approximately 10 pg/mL to 70 mg/mL) over the initial 2-4 weeks of treatment before declining to about 50 pg/mL and there were no meaningful differences in IL-6 levels between the 3 TCZ exposure groups. sIL-6R levels slowly increased and reached maximum levels 2-3 months after treatment initiation and, in contrast to IL-6, sIL-6R levels were increased as exposure to TCZ increased.
- There were no differences in the distributions of $C_{trough}52$ for patients in the active TCZ treatment arms who achieved and did not achieve sustained remission up to Week 52, nor was there a significant relationship between exposure and probability of REMI52.

- The fraction of patients in remission was lowest in the placebo group and it was highest and similar in the 2 groups who experienced the highest exposure to TCZ. In the lowest TCZ exposure group, this fraction was similar to the placebo arm during the first 3-4 months of treatment, but reached the remission rate of the other 2 exposure groups by the end of the treatment period.
- ARR52 and CCD were highest in the group receiving placebo, whereas, they were lower in patients receiving TCZ.
- PGA VAS score decreased in all of the treatment groups, including placebo and there were no differences in the magnitude of decrease between the 3 TCZ exposure groups. PCS increased slightly in the TCZ exposure groups, whereas, it was unchanged in the placebo group.
- On the whole, the occurrence of SAEs, II AEs, GI AEs and neutropaenia were not correlated with TCZ exposure.
- White blood cell counts declined in all of the treatment groups, including placebo, with the largest (and a similar) decline identified in the 2 upper tertiles of TCZ exposure.
- LDL cholesterol levels were unaffected by placebo, whereas, they were mildly increased in the TCZ treatment groups; however, the increases did not appear to be dependent on TCZ exposure.
- Overall, the beneficial PD effects and efficacy of TCZ improved with increasing TCZ exposure and therefore QW-dosing may be more beneficial than Q2W-dosing as it generally results in higher exposure in patients with GCA. In regards to safety, although there appears to be a relationship between decreased white blood cell counts and higher TCZ exposure, on the whole the incidence of AEs and abnormal laboratory parameters did not appear to be associated with increases in TCZ exposure.

7. Dosage selection for the pivotal studies

7.1. Pharmacokinetics and pharmacodynamics: dose finding studies

Not applicable.

7.2. Phase II dose finding studies

Not applicable.

7.3. Phase III pivotal studies investigating more than one dose regimen

The pivotal Phase III Study WA28119 assessed the efficacy/ safety in 250 GCA patients and PK/PD (in a subset of 147 patients) of 2 dosing regimens of TCA: 162 mg SC TCZ once weekly (QW) or every other week (Q2W) in combination with a 26 week prednisone taper regimen. The rationale provided for selecting these doses was as follows:

TCZ 4 mg/kg and 8 mg/kg IV every 4 weeks (Q4W) are approved doses of TCZ in patients with adult RA. Of the 31 case reports of GCA patients who had been dosed with TCZ at the time of study start, 29 patients received 8 mg/kg IV every 4 weeks (in some cases the starting dose was 8 mg/kg every 2 weeks) and 2 patients 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). 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 normalisation 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.

The SC route of administration, via pre-filled syringe (PFS), was chosen over the IV route for the pivotal GCA study as it provides a more convenient route of administration in this elderly population of patients with GCA (for example, home administration, no requirement for venous access). The Phase III RA SC program evaluated 2 SC doses (162 mg QW and Q2W). 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 MRA227; Study NP22623) and was expected to also show a similar PK/PD profile in GCA patients. This dose was expected to deliver optimised 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.

7.4. Evaluator's conclusions on dose finding for the pivotal studies

The above rationale for dose selection for the pivotal Phase III study in GCA patients is valid.

8. Clinical efficacy

8.1. Studies providing evaluable efficacy data

Indication 1: Treatment of giant cell arteritis (GCA) in adult patients.

Pivotal Study WA28119: Phase III, multicentre, randomised, double blind, placebo controlled study to assess the efficacy and safety of tocilizumab in subjects with GCA.

Other studies: Study ML25676 (Villiger, 2016) data from this study using IV TCZ was included to provide supportive evidence of efficacy/ safety of TCZ in treatment of GCA. However, the original CSR was not provided for evaluation.

8.2. Pivotal or main efficacy studies

8.2.1. Study WA28119

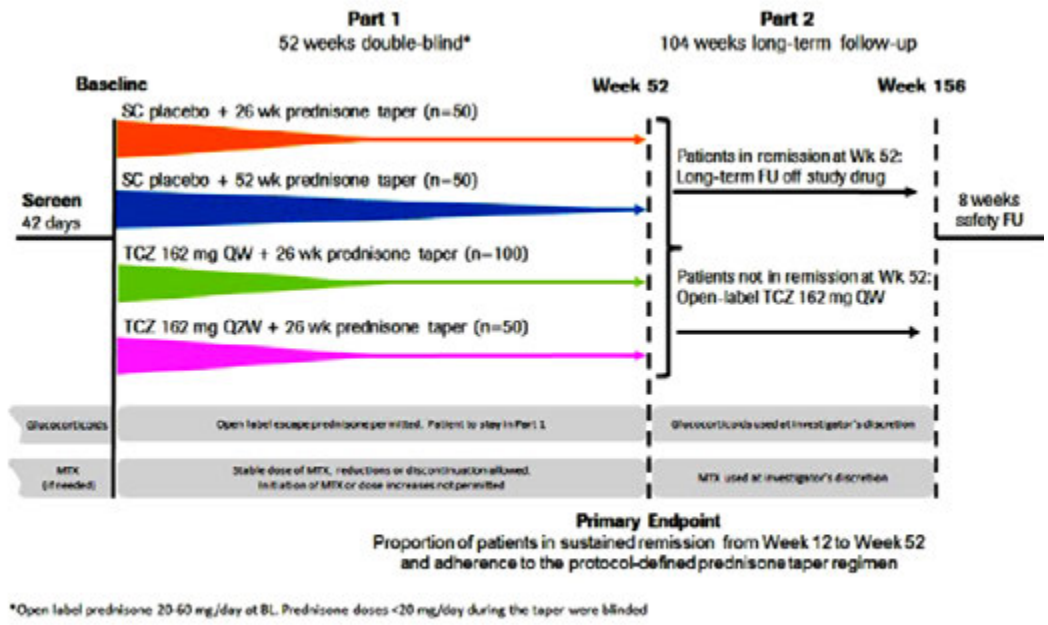
8.2.1.1. *Study design, objectives, locations and dates*

It was a Phase III, multicentre, randomised, 4-arm, double blind, placebo controlled study. 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. The overall study design is shown in Figure 6. The primary objective was to evaluate the efficacy of tocilizumab (TCZ) compared to placebo, in combination with a 26 week prednisone taper regimen, in patients with giant cell arteritis (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. The key secondary objective was to evaluate the efficacy of TCZ in combination with a 26 week prednisone taper regimen versus placebo in combination with a 52 week prednisone taper regimen 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 endpoints were 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 CS dose, effect on patient's quality of life, PKs and PDs of TCZ in patients with GCA. The exploratory objectives were to assess: - maintenance of remission after treatment with TCZ by evaluating the proportion of patients who remain in sustained remission at 64 weeks (and every 12 weeks thereafter); -the efficacy of TCZ as measured by the

annualised relapse rate, the remission rates over time, effect on PRO (by FACIT-Fatigue and EQ-5D scores) and effect of TCZ on the duration of CS use by treatment group. The study also evaluated safety and tolerability and immunogenicity of TCZ in combination with a 26 week prednisone taper regimen.

The study was conducted at 76 centres (Europe 61 centres; North America 15 centres) in 14 countries from 22 July 2013 to 11 April 2016.

Figure 6: Study WA28119. Study design



BL, baseline; FU, follow up; MTX, methotrexate; QW, weekly; Q2W, every other week; SC, subcutaneous; TCZ, tocilizumab.

8.2.1.2. *Inclusion and exclusion criteria*

The target population for this study included adult patients with GCA who had active disease within the 6 weeks prior to the baseline visit. New-onset and relapsing GCA patients were eligible. To ensure a balance of patients across treatment groups, patients were stratified according to whether they were on a high initial (baseline) prednisone dose (> 30 mg/day) or a low initial prednisone dose (≤ 30 mg/day). The proportion of relapsing patients was to be preferentially limited to 70% to ensure some enrolment of new-onset patients. The proportion of relapsing patients could be increased dependent on the rate of enrolment of relapsing versus new-onset patients.

The main inclusion criteria were:

1. Diagnosis of GCA classified according to the following criteria: Age ≥ 50 years; History of ESR ≥ 50 mm/hour[5] AND at least one of the following:

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

[5] 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).

- 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

2. New-onset or relapsing active disease defined as follows:

- New-onset: diagnosis of GCA within 6 weeks[6] 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 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.

3. Informed consent.

The main exclusion criteria related to Prior or Concomitant Therapy were:

- Treatment with any investigational agent within 12 weeks (or 5 half-lives of the investigational drug, whichever was longer) of screening
- Previous treatment with cell-depleting therapies, including investigational agents, including but not limited to alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19 and anti-CD20
- Treatment with IV gamma globulin or plasmapheresis within 6 months of baseline
- Previous treatment with alkylating agents, such as chlorambucil, or with total lymphoid irradiation
- Previous treatment with TCZ
- Immunisation with a live/attenuated vaccine within ≤ 4 weeks prior to baseline
- Treatment with hydroxychloroquine, cyclosporine A, azathioprine, or mycophenolate mofetil (MMF) within 4 weeks of baseline
- Treatment with etanercept within 2 weeks; infliximab, certolizumab, golimumab, abatacept or adalimumab within 8 weeks; or anakinra within 1 week of baseline.
- Previous treatment with tofacitinib.
- Treatment with cyclophosphamide within 6 months of baseline.
- 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.

Other general, safety-related and laboratory exclusion criteria are summarised**.**

[6] 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

8.2.1.3. *Study treatments*

Patients were screened up to 6 weeks (42 days) prior to the baseline randomisation visit. During the screening period, patients could receive glucocorticoids (GC) for the treatment of GCA at the discretion of the investigator. By the end of the screening period patients were to be able 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 were switched from the GC prescribed by the investigator to prednisone provided by the sponsor. The baseline daily dose had to be within the range of prednisone 20 to 60 mg/day depending on the investigator's assessment of the patient's disease activity and disease status and according to the protocol-defined prednisone taper schedule. The prednisone tapering was performed in an open-label fashion up to and inclusive of the daily dose of 20 mg/day and was then switched to double blind for dosages below 20 mg/day through to 0 mg.

Patients were randomised at Baseline 1:1:2:1 to 4 groups: short-course prednisone (26 week prednisone taper + weekly subcutaneous (SC) placebo (PBO + 26 wk)); long-course prednisone (52 week prednisone taper + weekly SC placebo (PBO + 52 wk)); weekly SC TCZ 162 mg + 26 week prednisone taper (TCZ QW); every other week SC TCZ 162 mg + 26 week prednisone taper (TCZ Q2W).

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. The recommended injection sites were uninvolved areas of skin at the front of the middle thighs and the lower part of the abdomen below the navel (belly button), except for the 5-cm area directly around the navel. If a caregiver was giving the injection, the outer area of the upper arms could also be used. Injections were never to be made into areas where the skin was not intact or was tender, bruised, red, or hard. Subcutaneous injections were to be administered on the same day every week, whenever possible. If for any reason the weekly schedule could not be kept (for example, SC injections had to be administered to patients during a site visit), the following minimum and maximum intervals between the blinded weekly injections were to be followed: 5-day minimum interval and 11-day maximum interval. After the 11-day maximum interval had passed, the dose was considered to have been missed and the next dose taken was to be the next scheduled dose as per the schedule of assessments. The first 4 SC injections (administered once weekly) in the double blind period had to be administered to patients under close supervision of the investigator in a setting where medications and resuscitation facilities were available and patients were required to stay at the sites for approximately 2 hours following each SC injection. Patients and caregivers were trained to perform the SC injections at the initial treatment[7]. For all patients, whenever pre-dose PK and PD sampling were scheduled, SC injections were administered to patients after samples were taken at the clinic site.

Open-Label TCZ SC (Part 2): Patients with persistent disease activity or those who experienced flares after induction of remission during the double blind period had the option to receive open-label TCZ (162 mg QW). The duration of open-label therapy up to a maximum of 104 weeks was determined by the investigator according to the patient's clinical condition. Open-label study drug (TCZ) was supplied in 1-mL, ready-to-use, single-use PFS, each delivering 162 mg (0.9 mL) of TCZ solution.

All treatment groups followed either a short or long *prednisone taper regimen* according to a defined schedule during Part 1 of the study. Prednisone/placebo tablets/capsules were taken

[7] After the first 2 injections, once the patient or the patient's caregiver had demonstrated competence in giving the injection correctly, SC injections could be administered by the patient or the patient's caregiver at the site. Once the patient or the patient's caregiver had demonstrated competence in giving the injection after the first 4 visits, SC injections could be administered at home. If a patient was unable or did not wish to administer study drug at home, clinic staff could administer the injections to the patient.

daily by the patient for the entire 52 week period regardless of the randomised assignment of the patient to either the short or the long taper regimen. At the baseline visit of the 52 week double blind period, all patients had to be taking prednisone 60 mg/day, 50 mg/day, 40 mg/day, 35 mg/day, 30 mg/day, 25 mg/day, or 20 mg/day in order to start the protocol-defined prednisone tapering schedule. There were 2 phases to the prednisone taper regimen:

- Open-label phase, for dosages from 60 mg/day to 20 mg/day: Open-label prednisone was given to patients while their prednisone dose was being tapered down from 60 mg/day to 20 mg/day.
- Blinded phase, for dosages < 20 mg/day: During the prednisone taper blinded phase (< 20 mg/day), patients were supplied with weekly blister packs with clearly marked daily doses. Depending on a patient's assignment to either the long or short taper regimen, the daily dose could contain prednisone capsules, placebo capsules, or a combination of the 2. The number of capsules taken each day could vary and might have increased or decreased during the tapering schedule but never exceeded 5 capsules per day.

Continuous Assessment of Adherence to Prednisone Taper: At every visit, an assessment of patient's disease was made to assess if the patient could adhere to the prednisone tapering schedule. If a patient had no flare of GCA and was able to follow the tapering schedule, the patient continued in the double blind period of the study. If the patient experienced a disease flare or could not adhere to the prednisone tapering schedule, the patient had to stop the protocol-defined prednisone taper and instead could receive escape prednisone therapy. Glucocorticoid use during the open-label extension period of the study (Part 2) was at the discretion of the investigator.

Concomitant medications: Patients in all arms were to be treated with anti-platelet therapy (aspirin or clopidogrel) according to local practice and at the discretion of the investigator. To prevent glucocorticoid-induced osteopaenia/osteoporosis, patients were to receive oral calcium and 25-hydroxy vitamin D supplementation unless contraindicated (calcium 1200-1500 mg and vitamin D 800-1000 IU daily in divided doses). In addition, unless contraindicated, bisphosphonate therapy (for example alendronate 70 mg weekly or zoledronate 4 mg annually) was to be administered at the discretion of the investigator. The use of lipid lowering agents in patients with elevated lipids was strongly encouraged in conjunction with the investigator's clinical judgment and guidelines. Short-term glucocorticoids could be administered in addition to the protocol-defined prednisone taper regimen, for the management of events such as serious infection or when additional glucocorticoids might be required to prevent adrenal insufficiency.

Methotrexate could be started prior to screening, but the dose was to remain stable and not be increased through screening and during the double blind period (Part 1) of the study. During the study the MTX dose could be reduced or discontinued if necessary for safety reasons or if, in the opinion of the investigator, it was no longer required to treat the patient's GCA. Methotrexate could be initiated or adjusted at the discretion of the investigator during the open-label/long-term follow-up period (Part 2).

Treatment compliance: A drug receipt record and drug dispensing log were maintained and used to assess accountability of the investigational medicinal product. Patient compliance was assessed by maintaining adequate drug dispensing logs, patient diaries (for SC home injections) and return records.

8.2.1.4. *Efficacy variables and outcomes*

Assessment of GCA disease activity was based on the presence or absence of signs and symptoms, assessment of acute phase reactants (ESR and CRP) and assessment of prednisone dose and duration. During the 52 week double blind treatment period, patients had visits at Weeks 1, 2, 3 and 4, and then every 4 weeks. At every visit the patient was assessed to determine disease activity and whether the patient could continue to adhere to the protocol-

defined prednisone taper schedule (or not, due to GCA disease flare or other reasons). To be considered for sustained remission of GCA, induction of remission had to occur within 12 weeks of baseline. Patients not in remission after 12 weeks were considered as non-responders in the analyses.

The primary endpoint of the study, the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined prednisone taper regimen, was evaluated after all patients had completed the 52 week double blind phase of the study (Part 1). Induction of remission had to occur within 12 weeks of randomisation. Remission was defined as the absence of flare[8] and normalisation of the CRP (< 1 mg/dL). Sustained remission was defined as absence of flare following induction of remission up to the 52 week time point.

The key secondary analysis compared the proportion of patients in sustained remission at Week 52 in each TCZ treatment group versus the placebo group with 52 week prednisone taper. Other secondary endpoints included: Time to first GCA disease flare after clinical remission up to Week 52 and Total cumulative prednisone dose over 52 weeks.

The following exploratory efficacy endpoints were summarised descriptively: Annualised Relapse Rate, Remission Rate over Time, Duration of Glucocorticoid Use and Sustained Remission at Week 52 – Excluding Adherence to Prednisone Taper.

The patient reported outcomes (PROs) included Patient's Global Assessment (PGA)[9], SF-36 (Short Form-36 Questionnaire)[10], EQ-5D (EuroQoL 5-D)[11] and FACIT-Fatigue[12].

8.2.1.5. *Randomisation and blinding methods*

Eligible patients who fulfilled the inclusion and exclusion criteria were randomised in a 1:1:2:1 ratio to the following treatment groups for 52 weeks:

- SC placebo + 26 week prednisone taper regimen (PBO + 26 wk)
- SC placebo + 52 week prednisone taper regimen (PBO + 52 wk)
- 162 mg of SC TCZ QW + 26 week prednisone taper regimen (TCZ QW)
- 162 mg of SC TCZ Q2W + 26 week prednisone taper regimen (TCZ Q2W)

Patients were randomised utilising an interactive voice response system (IVRS). Randomisation was stratified by baseline prednisone dose (≤ 30 mg/day or > 30 mg/day). 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

[8] Flare was determined by the investigator and was defined as the recurrence of signs or symptoms of GCA and/or ESR ≥ 30 mm/hr attributable to GCA. o Patients had to follow the protocol-defined prednisone taper regimen.
[9] The Patient's Global Assessment (PGA) of disease activity was assessed on a 100-mm horizontal visual analog scale (VAS).
[10] The SF-36 (Version 2) is a standardised questionnaire consisting of 36 questions used to assess a patient's health across 8 dimensions: • General health• Mental health• Physical functioning• Social functioning• Vitality questions• Bodily pain
• Role limitation due to physical function• Role limitation due to emotional function
[11] The EQ-5D is a generic utility measure used to characterise current health states. This self-reported questionnaire consists of 2 pages comprising the EQ-5D descriptive system and the EQ-5D VAS. The EQ-5D descriptive system comprises 5 dimensions of health that can be converted to a single index utility score. The EQ-5D VAS is neither part of the scoring algorithm nor appropriate for assessing efficacy; this VAS score is not presented.
[12] The FACIT-Fatigue questionnaire is a self-administered patient questionnaire that consists of 13 statements designed to measure the degree of fatigue experienced by the patient in the previous 7 days. For each question there are 5 possible responses: 0 (not at all), 1 (a little bit), 2 (somewhat), 3 (quite a bit), 4 (very much). Statements 1–6 and 9–13 are worded so that higher scores correspond to greater fatigue, while statements 7 and 8 are worded so that higher scores correspond to less fatigue. All scores, except those for statements 7 and 8, will therefore be 'reversed' on the 0 to 4 scale (i.e., a response of 0 will receive a score of 4, a response of 1 will receive a score of 3, etc.), so that for all questions higher scores reflect improvement.

within 6 weeks of the baseline visit) but could be increased depending on the rate of enrolment of relapsing versus new-onset patients.

The study was blinded during the first 52 weeks and to maintain the blinding of treatment allocation a Dual Assessor Approach was utilised. A Clinical Assessor was designated who assessed the patient for signs and symptoms of GCA and managed the prednisone taper/escape prednisone at each visit. 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 also 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. The Laboratory Assessor was permitted to discuss ESR elevations pre-specified in the Dual Assessor Manual with the Clinical Assessor as required for clinical management of the patient. CRP levels were determined by a central laboratory and the results from assessments carried out during Part 1 were blinded to the sponsor, all site and study staff throughout the study. 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 SAEs that were considered by the investigator to be related to study drug. Unblinding was performed through the IVRS. Following unblinding, decisions for withdrawal of patients from the study were at the investigator's discretion. Patients who were withdrawn were then to be followed per protocol.

8.2.1.6. *Analysis populations*

All-Patients Population: The all-patients population included all patients randomised in the study. Disposition summaries were based on the all-patients population.

Intent-to-Treat (ITT) Population: The primary analysis population for all efficacy analyses was the ITT population which included all patients randomised into the study who received at least one TCZ/placebo injection. The treatment group for this population was defined according to the treatment assigned at randomisation by the IVRS.

Pharmacokinetic-Evaluable Population: The PK-evaluable population included all patients who received at least one TCZ injection and had at least one PK sample with detectable results taken at any time during the study (up to Week 52 for the primary data cut).

Escape Population: Depending on the proportion of escape patients at Week 52, a limited number of analyses could be performed on the subset of patients who received escape therapy. The escape population included all patients who received at least one administration of TCZ/placebo SC study drug, entered escape therapy and received at least one dose of escape prednisone medication.

Safety Population: Analysis of safety data was based on the safety population which included all patients who received at least one administration of study drug and provided at least one post-dose safety assessment (withdrawal, adverse event (AE), death, laboratory assessment, or vital sign assessment). Patients were summarised according to the treatment they actually received.

8.2.1.7. *Sample size*

A sample size of 100 patients in the 162 mg TCZ QW group and 50 patients in both the 162 TCZ Q2W group and PBO + 26 week group (in combination with the 26 week prednisone taper group) ensured 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 overall alpha level of 0.01 (2-sided). This assumed that the absolute difference in the proportion of patients who were in sustained remission at Week 52 was equal to 40% (assuming 70% and 30% remission rates in the TCZ and placebo groups respectively). In addition, 50 patients were also included in a PBO + 52 week prednisone taper group.

8.2.1.8. *Statistical methods*

The primary and key secondary endpoints were tested at a 1% overall significance level (α = 0.01) against 2-sided alternatives. There were 2 independent hierarchies for the TCZ dose families for which the overall alpha level was equally divided in order to correct the type I error rate for multiple comparisons. Both hierarchies tested the treatment comparisons in a fixed sequential order 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. Claims of statistical significance were not to be made on the key secondary endpoint if its preceding test for superiority did not yield a significant p-value (< 0.005).

The primary analysis tested the null hypothesis that the proportion of patients in sustained remission at Week 52 on TCZ in combination with the 26 week prednisone taper regimen was the same as the proportion of patients in sustained remission at Week 52 on placebo in combination with the 26 week prednisone taper regimen. The null hypothesis was rejected if the proportion of patients in sustained remission differed between the TCZ and placebo groups.

The TCZ treatment groups were compared with the placebo group (in combination with the 26 week prednisone taper group) using a Cochran-Mantel-Haenszel test, adjusting for starting prednisone dose (≤ 30 mg/day, > 30 mg/day).

The primary endpoint, proportion of patients in sustained remission at Week 52, was analysed using a Cochran-Mantel-Haenszel (CMH) test, adjusting for starting prednisone dose (≤ 30 mg/day, > 30 mg/day), which was the stratification factor applied at randomisation. Non-responder imputation was used for missing data. Patients who had a flare or received escape therapy, who did not adhere to the prednisone taper regimen, who withdrew from the study prior to Week 52, who had elevated CRP values at 2 consecutive study visits from Week 12 onwards, or for whom a remission status could not be determined at Week 52, were classed as non-responders in the primary analysis. Patients who did not achieve remission within 12 weeks of baseline were also classed as non-responders in the primary analysis.

Sensitivity Analyses: To assess the robustness of the primary endpoint, a tipping point analysis was performed. The tipping point was defined as the difference in the number of missing events between the treatment groups that result in a change in the primary outcome conclusions (Yan et al. 2009). A 2-dimensional plot was produced for each primary comparison of TCZ + 26 week prednisone taper to placebo + 26 week prednisone taper, to evaluate where the tipping point lies. The tipping point analysis was used to assess truly missing data for sustained remission only. Escape patients continued to be classed as non-responders. Withdrawal patients who had a GCA flare prior to withdrawal were also classed as non-responders as this represents the true outcome had they remained in the study. Withdrawn patients who did not experience a GCA flare prior to withdrawal were classed as missing and were sequentially imputed for the tipping point analysis.

A second sensitivity analysis was performed on the basis of only signs and symptoms of disease (excluding the requirement for normalised CRP < 1 mg/dL from the definition for remission) 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 analysis compared the proportion of patients in sustained remission at Week 52 in each TCZ treatment group versus the placebo group with 52 week prednisone taper. The treatment effect for each comparison was assessed by means of a non-inferiority test based on the ITT population. In order to determine non-inferiority, a 2 sided 99.5% CI was constructed for the difference in proportions between each TCZ group and the placebo group. Non-inferiority was assumed if the lower bound of the 2-sided 99.5% CI was ≥ -22.5%. This non-inferiority margin allowed for preservation of at least 50% of a minimum treatment effect of 45% observed with corticosteroid therapy alone. Assumptions for a 45% minimum treatment effect included a response rate of 0% (95% CI: 0, 7) for placebo (based on the observation that GCA very rarely remits spontaneously) and a response rate of 71% (95% CI: 52, 86) for a 52 week steroid taper regimen (observed in a randomised controlled study of adalimumab versus prednisone (Seror et al. 2014)). This results in a minimum treatment effect of 45% when calculating the difference between the upper limit of the placebo response rate (7%) and the lower limit of the 52 week steroid taper response rate (52%). This was considered to be the most conservative estimate of the standard of care treatment response given the information available.

Other secondary endpoints: (1) Time to first GCA disease flare after clinical remission up to Week 52 was summarised by Kaplan-Meier curves, the median, 25th and 75th percentiles (where possible) and 99% CI for the median. The treatment groups were compared using a Cox proportional hazards model adjusting for the stratification factor applied at randomisation. Patients who withdrew from the study prior to Week 52 were censored from the time of withdrawal. (2) Total cumulative prednisone dose over 52 weeks was analysed using a van Elteren test stratified by starting prednisone dose. The median total cumulative prednisone dose[13] over the 52 weeks for each treatment group and the corresponding 95% CI for the median are presented. Other secondary endpoints were not formally tested; however exploratory p-values were provided for the comparisons between each of the TCZ groups and both placebo groups. The following exploratory efficacy endpoints were summarised descriptively: Annualised Relapse Rate, Remission Rate over Time, Duration of Glucocorticoid Use and Sustained Remission at Week 52 – Excluding Adherence to Prednisone Taper.

Analysis of PROs: Change from Baseline in PGA was analysed using a maximum likelihood-based repeated measures model. The analysis included the 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. Change from Baseline to Week 52 in the SF-36 was analysed using a maximum likelihood-based repeated measures model. The change from Baseline in MCS and PCS at Week 52 was calculated for each as the score at Week 52 minus the baseline score. The MCS and PCS as well as the changes from Baseline at each visit were summarised descriptively.

Subgroup Analyses: The proportion of patients in remission and in sustained remission by visit was summarised descriptively for the following subgroups, with further investigation being carried out if required. Unless considered to be of major clinical relevance, subgroup analyses were only performed for subgroups where there was a minimum of 20% of patients from the overall population.

- Disease onset at Baseline (new-onset, relapsing) Starting prednisone dose (5 mg intervals) was also summarised descriptively for this subgroup
- Starting prednisone dose (≤ 30 mg/day, > 30 mg/day)

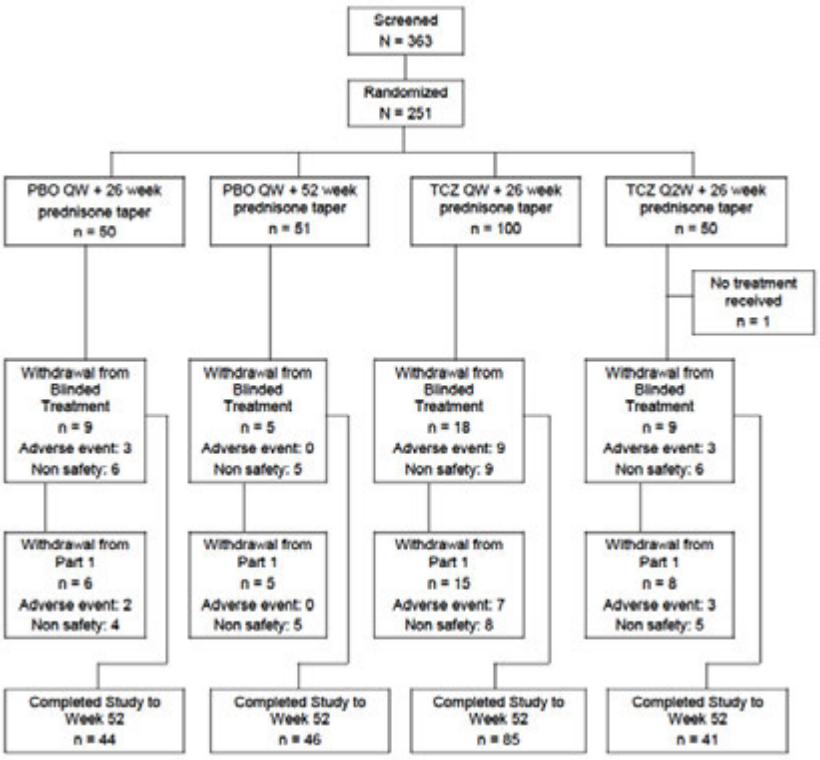
[13] For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) were assumed to be the minimum dose tablet(s) available from that pack, which resulted in a conservative overestimation of prednisone dose on all treatment arms.

- Previous history of remission, relapsing patients only (yes, no)
- Positive imaging AND negative/no Temporal Artery Biopsy (TAB) AND no cranial symptoms at diagnosis (yes, no)
- GCA diagnosis meeting the ACR[14] criteria (yes, no).

8.2.1.9. *Participant flow*

Of the 363 patients screened, a total of 251 patients were randomised into the study. The main reasons for screening failure were absence of a diagnosis of GCA per protocol-specified criteria (24 patients) and inability or unwillingness to provide written informed consent (24 patients). Other reasons included absence of new-onset or relapsing active disease as defined in the protocol (10 patients) and ALT or AST levels outside the protocol-specified range (6 patients) (Figure 7). During the 52 week double blind period (Part 1), a total of 41 of the 251 randomised patients were withdrawn prematurely from blinded study treatment (TCZ/placebo/prednisone): 9 patients (18%) in the PBO + 26 week group, 5 patients (10%) in the PBO + 52 week group, 18 patients (18%) in the TCZ QW group and 9 patients (18%) in the TCZ Q2W group. Of the 251 patients randomised into the study (100 patients to the TCZ QW group, 50 patients to the TCZ Q2W group, 50 patients to the PBO + 26 week group and 51 patients to the PBO + 52 week group), 250 patients received the treatment to which they were assigned. One patient [information redacted] who was randomised to the TCZ Q2W group withdrew the same day they were randomised and did not receive any study treatment. This patient was excluded from the safety and intent-to-treat (ITT) efficacy analysis populations.

Figure 7: Overview of patient disposition



[14] Where ACR 1990 criteria for diagnosis of GCA were defined as having 3 out of the following 5 symptoms: aged ≥ 50 years, ESR ≥ 50 mm/hour, new-onset localised headache, temporal artery abnormality, abnormal artery biopsy (i.e., positive TAB).

8.2.1.10. *Major protocol violations/deviations*

Inclusion/exclusion violations identified for patients entering the study were summarised. One additional patient (in the PBO + 52 week group) was mistakenly enrolled in the study with PMR (rather than GCA with PMR symptoms) and was withdrawn from the study by the sponsor on discovery that the patient did not have a diagnosis of GCA. Five patients deviated from the protocol-defined prednisone tape. Patients who deviated from the protocol defined prednisone taper were placed back[15] onto the prednisone dose they should have been receiving. None of the violations/ deviations identified was considered to have affected the integrity of the study results.

8.2.1.11. *Baseline data*

Majority of the patients were Caucasian (96.8%) females (74.9%), with a mean age of 69 years (more than 2-thirds of patients in each treatment group were aged ≥ 65 years. The treatment arms were balanced with respect to all baseline demographic characteristics recorded with the exception of smoking status, where a higher percentage of non-smokers was observed in the PBO + 26 week group (70%) compared with the other treatment groups (57% in each group).

Overall, 96% of patients were enrolled into the study based on historical ESR ≥ 50 mm/hr while the remainder had a history of CRP ≥ 2.45 mg/dL and qualified on that basis. GCA disease features were generally well balanced between the treatment groups. New-onset localised headache and PMR symptoms were the most common clinical manifestations, reported by 67% and 62% of patients, respectively. Jaw claudication (otherwise unexplained mouth or jaw pain upon mastication) and scalp tenderness were reported in approximately one-third of patients. Temporal artery tenderness was observed in 29%, decreased temporal artery pulsation in 12% and ischemia-related vision loss in 10% of patients.

Imaging was performed in 139 (55%) patients (PET-CT most common being performed in 70%; 97/139); 115 of the 139 patients who underwent imaging (83%) had a positive result consistent with a diagnosis of large-vessel GCA (94 of these 115 patients had a positive imaging result only, with either no TAB performed or a negative TAB). Of these, 42 patients had no cranial symptoms of GCA at diagnosis (18, 9, 8 and 7 patients in the TCZ QW, TCZ Q2W group, PBO + 26 week and PBO + 52 week groups, respectively); 22 patients had both a positive imaging result and a positive temporal artery biopsy test result. Temporal artery biopsy was performed in 172/251 (69%) patients and was positive in 91% (156/172) of these patients. Of the 156 patients with a positive TAB result, 134 patients were TAB-positive only (that is, 22 patients had both positive TAB and a positive imaging result.

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 (that is, 60/50/40/35/30/25 or 20 mg/day). However, 5 patients received the incorrect dose of prednisone at Baseline in error (1 patient in the PBO + 52 week group, 2 patients each in the TCZ Q2W and the TCZ QW groups). These prednisone starting dose errors were captured as major protocol deviations, although the patients were permitted to remain in the study (refer to Section 7.2.1.10 above). Two further patients had prednisone dosing medication errors at Baseline: A patient in the PBO + 52 week group took 28.5 mg/day prednisone (that is, 200 mg over 7 days) and another patient in the TCZ QW group took 10 mg/day prednisone. These prednisone medication errors were not captured as protocol

[15] 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.

violations. All but one[16] 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.

The median duration of GCA at Baseline was 52, 41.5, 80 and 53 days in the in the TCZ QW, TCZ Q2W group, PBO + 26 week and PBO + 52 week groups, respectively.

Comment: It is important to note that the median duration of GCA at Baseline was much longer in the PBO + 26 week group (80 days) compared to the other groups (41-53 days) although it was difficult to interpret significance of this difference considering the wide range of values in all groups. Furthermore, effect of GCA duration on efficacy results was not explored.

Overall, treatment arms were balanced with respect to GCA disease characteristics. ESR and CRP were within normal ranges for the majority of patients at Baseline because of high dose glucocorticoid use during screening. Relapsing disease patients comprised 53% of the study population with 47% of patients presenting with new-onset disease; 38% (95/251) of patients had cranial symptoms only at Baseline, 21% (52/251) had PMR symptoms only and 41% (104/251) of the patients patients) had both cranial and PMR symptoms at Baseline. Vision impairment was reported in a small number of patients at Baseline: Blurred vision was reported for 14 patients (6%) with amaurosis fugax reported in 1 patient in each of the TCZ treatment groups. Unilateral blindness was reported in 1 patient in each treatment group and bilateral blindness was reported in a single patient in the TCZ Q2W group. Anterior arteritic ischemic optic neuropathy was reported in 1 patient in each of the TCZ treatment groups.

Previous/ongoing medical conditions suspected to be caused by prior glucocorticoid treatment (as determined by the investigator) were reported in 28%, 22%, 34% and 37% of patients in the TCZ QW, TCZ Q2W group, PBO + 26 week and PBO + 52 week groups, respectively. The most commonly reported individual medical conditions considered related to glucocorticoid treatment were insomnia (11 patients overall), osteoporosis (9 patients overall), diabetes mellitus (9 patients overall) and hypertension (6 patients overall). Medical conditions which started prior to screening and were present at Baseline (other than GCA) were reported in 96%, 94%, 100% and 98% of patients, respectively and the most common concurrent medical conditions were in the Musculoskeletal and Connective Tissue Disorders and Vascular Disorders SOCs, with osteoporosis and hypertension, respectively, being the most commonly reported conditions in these body systems.

Concomitant treatments for GCA (other than blinded study treatment) were reported for 67%, of patients in the TCZ QW and TCZ Q2W groups, 78% of patients in the PBO + 26 week group and 71% of patients in the PBO + 52 week group. Antimetabolites (methotrexate) were received by 11%, 10%, 16% and 18% of patients in the TCZ QW, TCZ Q2W group, PBO + 26 week and PBO + 52 week groups, respectively. Salicylates (aspirin) were taken by 18% of patients in the TCZ QW, TCZ Q2W and PBO + 26 week groups and 16% of patients in the PBO + 52 week group while analgesics (mainly paracetamol) were taken by 3%, 14%, 16% and 12% of patients in the TCZ QW, TCZ Q2W group, PBO + 26 week and PBO + 52 week groups, respectively.

Steroids (including low-dose glucocorticoid treatment) were the most commonly reported concomitant treatments for GCA. The use of steroids in addition to the protocol defined prednisone taper may appear high. These numbers must be interpreted in the context that they include also concomitant glucocorticoid medications which were stopped on Study Day 1 (prior to initiation of study medication) as well as concomitant medications for GCA in patients

[16] The patient flared at Week 1 but did not receive escape therapy at this visit; this patient subsequently flared at the Week 52 visit.

withdrawn from study treatment but who were being treated in safety follow-up. Other concomitant treatments for GCA were taken by no more than 2 patients in any treatment group.

8.2.1.12. *Results for the primary efficacy outcome*

The primary efficacy analysis was conducted in the ITT population. Patients who flared or received escape therapy, who did not adhere to the prednisone taper regimen (> 100 mg additional glucocorticoids), who had 2 consecutive CRP elevations (≥ 1 mg/dL), 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.

At Week 52, sustained remission was achieved in 56.0%, 53.1% and 14% of patients in the TCZ QW, TCZ Q2W and PBO + 26 week groups, respectively; 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, $p \leq 0.0001$) and that between the TCZ Q2W dose group and placebo was 39.1% (99.5% CI: 12.5 to 65.7, $p < 0.0001$). The study met its primary endpoint as both TCZ dose groups demonstrated clinical and statistical superiority over placebo.

In the sensitivity analysis (excluding the requirement for normalised CRP < 1 mg/dL from the definition of remission), sustained remission at Week 52 was achieved in 59.0%, 55% and 20% of patients in the TCZ QW, TCZ Q2W and PBO + 26 week groups, respectively; the difference in the percentage of responders between TCZ QW and placebo +26 week groups was 39.0% (99.5% CI: 14.8 to 63.2, $p < 0.0001$) and that between TCZ Q2W and placebo+26 week groups was 35.1% (99.5% CI: 7.8 to 62.4, $p = 0.0004$). A sensitivity analysis of the primary efficacy endpoint based on analysis of the proportion of patients achieving sustained remission at Week 52 regardless of adherence to the protocol-defined prednisone taper (that is, patients receiving > 100 mg additional prednisone dosing from Week 12 to Week 52 also showed similar results as both TCZ dose groups demonstrated statistical superiority over placebo; sustained remission rates were 59.0%, 53.1% and 14%, respectively; difference TCZ QW – placebo= 45% (99.5% CI: 20.9 to 69.1; $p < 0.0001$) and TCZ Q2W- placebo= 39.1% (99.5% CI: 12.5 to 65.7; $p < 0.0001$). An additional sensitivity analysis was performed where the primary efficacy endpoint analysis was repeated for patients who completed the study and were compliant[17] with study medication in comparison to the ITT population; sustained remission rates in this analysis were 64.4%, 62.5% and 14.8% in the TCZ QW, TCZ Q2W and PBO + 26 week groups, respectively; difference TCZ QW – placebo= 49.6% (99.5% CI: 15.6 to 83.7, $p < 0.0001$) and TCZ Q2W- placebo= 47.7% (99.5% CI:9.6 to 85.8, $p = 0.0005$).

A post-hoc analysis determined the percentage of patients meeting each individual criterion for not achieving sustained remission with results showing that higher proportions of patients flared and subsequently received treatment with escape prednisone in the placebo groups compared to the TCZ groups. 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; 8 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.

8.2.1.13. *Results for other efficacy outcomes*

The *key secondary endpoint* of 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 (56%, 53.1% and 17.6% in TCZ QW +26 week

[17] Patients were considered compliant with study medication if they received the expected number of SC TCZ/placebo doses and their dose was not ever modified.

taper, TCZ Q2W+26 week taper and placebo+52 week taper groups, respectively) was met for both TCZ doses; both demonstrated non-inferiority compared to treatment with SC placebo in combination with a 52 week prednisone taper (based on a non-inferiority margin of -22.5%, with the difference in response rates being 38.35% (99.5% CI: 17.89, 58.81) for TCZ QW and 35.41% (99.5% CI: 10.41, 60.41) for TCZ Q2W) and subsequently also demonstrated superior efficacy compared to PBO + 52 week ($p \leq 0.0002$). Sensitivity analyses were generally consistent with the key secondary efficacy analysis, with the TCZ QW dose group again showing a statistically significant superior treatment difference compared to PBO + 52 week across all analyses. The TCZ Q2W arm met non-inferiority for both the sensitivity analysis excluding the requirement for normalised CRP (< 1 mg/dL) from the definition of remission and the analysis of completers adhering to study medication (lower confidence limits: -5.46 and -1.40, respectively > -22.5 (non-inferiority margin)) but did not meet the pre-specified significance level for superiority ($p < 0.005$ for the key secondary endpoint) in either analysis. In the sensitivity analysis irrespective of adherence to the prednisone taper regimen, superiority for both TCZ doses compared with placebo was demonstrated (Table 12).

Table 12: Sensitivity analysis for primary efficacy endpoint Proportion of patients achieving sustained remission at Week 52 (TCZ versus PBO + 52 wk) excluding requirement for normalised CRP (< 1mg/dL) from definition of remission

	PBO QW + 52 Week Prednisone Taper N = 51	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Tap N = 49
Responders [a]	17 (33.3%)	59 (59.0%)	27 (55.1%)
Non-Responders [b, c]	34 (66.7%)	41 (41.0%)	22 (44.9%)
Unadjusted difference in response rates		25.67	21.77
99.5% CI		(2.56, 48.77)	(-5.46, 48.99)
p-value (Cochran-Mantel-Haenszel) [d, e, f]		0.0030	0.0292

Table 21 Sensitivity Analysis: Proportion of Patients Achieving Sustained Remission at Week 52 (TCZ versus PBO + 26 wk) – Regardless of Adherence to the Protocol-defined Prednisone Taper Regimen

	PBO QW + 52 Week Prednisone Taper N = 50	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
Responders [a]	9 (17.6%)	59 (59.0%)	26 (53.1%)
Non-Responders [b]	42 (82.4%)	41 (41.0%)	23 (46.9%)
Unadjusted difference in response rates		41.35	35.41
99.5% CI		(20.98, 61.73)	(10.41, 60.41)
p-value (Cochran-Mantel-Haenszel) [c, d, e]		< 0.0001	0.0002

Table 22 Sensitivity Analysis: Proportion of Patients Achieving Sustained Remission at Week 52 (TCZ versus PBO + 52 wk) - Patients who Completed the Study and were Compliant with Study Medication

	PBO QW + 52 Week Prednisone Taper N = 23	TCZ QW + 26 Week Prednisone Taper N = 45	TCZ Q2W + 26 Week Prednisone Taper N = 24
Responders [a]	6 (26.1%)	29 (64.4%)	15 (62.5%)
Non-Responders [b, c]	17 (73.9%)	16 (35.6%)	9 (37.5%)
Unadjusted difference in response rates		38.36	36.41
99.5% CI		(5.77, 70.94)	(-1.40, 74.23)
p-value (Cochran-Mantel-Haenszel) [d, e, f]		0.0035	0.0127

Patients were in sustained remission when they were responders from Week 12 to Week 52.

Elevated ESR attributed to GCA was reflected in flare by the investigator.

Patients who flared, moved to escape medication or withdrew prior to Week 52 were classed as non-responders.

Patients who had received > 100 mg additional glucocorticoid dosing from Week 12 to Week 52 were considered as not having adhered to the protocol-defined prednisone taper regimen.

Patients were considered compliant with study medication if they received the expected number of TCZ doses and their dose was not ever modified.

[a] Patients in remission were classed as responders.

[b] Patients with elevated CRP whose next CRP value was elevated or missing were classed as non-responders.

[c] Patients not adhering to the protocol-defined prednisone taper were classed as non-responders.

[d] Non-inferiority comparison uses unpooled SE.

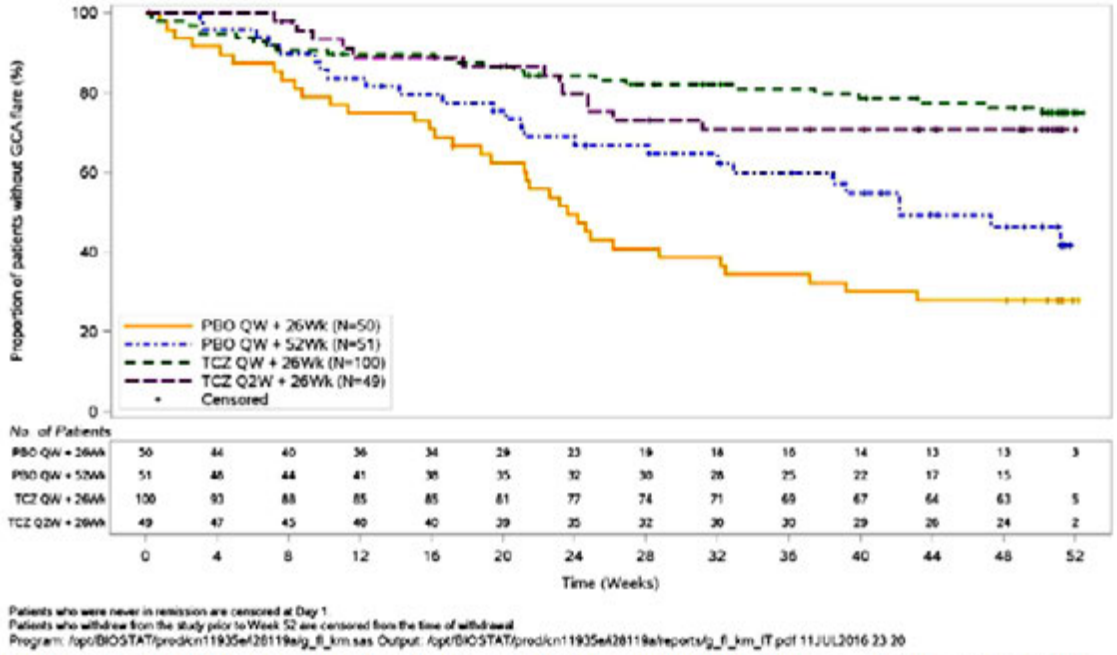
[e] Stratification factor, starting prednisone dose (≤ 30 mg/day, >30 mg/day) was included in the model.

[f] Analysis adjusted for the randomization stratification factor applied at baseline.

Other secondary endpoints: The proportion of patients with GCA flare was 69%, 49%, 23% and 26.5% in the placebo+26 week taper, placebo+52 week taper, TCZ QW +26 week taper, TCZ Q2W+26 week taper groups, respectively. The median time to GCA disease flare following clinical remission was 165 days in the PBO + 26 week group and 295 days in the PBO + 52 week group. Median time to GCA disease flare was not calculable in the TCZ QW and TCZ Q2W groups by Week 52 due to fewer than 50% of patients having experienced a flare by Week 52.

Time to event analysis showed a statistically significantly lower risk of GCA disease flare in both TCZ dose groups compared to the PBO + 26 week group; HRs were 0.23 (99% CI: 0.11 to 0.46; $p < 0.0001$) for the TCZ QW group and 0.28 (99% CI: 0.12 to 0.66; $p < 0.0001$) for the TCZ Q2W group (Figure 8).

Figure 8: Kaplan Meier plot of Time to first GCA flare (ITT)



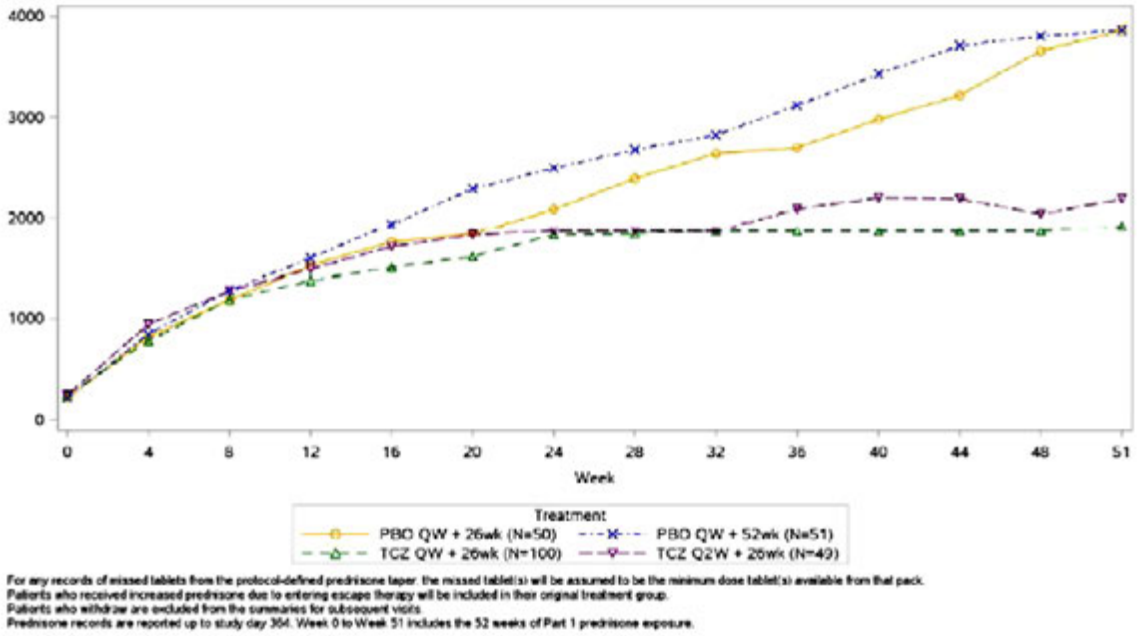
Note: the low number of patients at risk at Week 52 is due to the method used to calculate the Week 52 time window. The majority of patients completed their Week 52 visit in the few days prior to the end of the window and are therefore censored at the very end of the Week 52 window. This does not impact the results in any way and is applied consistently across all patients and groups.

An additional ad-hoc sensitivity analysis of time to first symptomatic GCA flare was performed excluding flares due to ESR elevations only (that is, excluding flares in the absence of other signs and symptoms of GCA). In this analysis, median time to GCA disease flare following clinical remission was 183 days in the PBO + 26 week group and 331 days in the PBO + 52 week group. Consistent with the ITT analysis, median time to GCA disease flare was not calculable in the TCZ QW and TCZ Q2W groups. The summary of the signs and symptoms at any time showed a similar profile across all 4 treatment groups. The proportions of patients with signs and symptoms during the study were lower in the TCZ QW group compared to the other treatment groups. The symptoms most frequently reported were cranial symptoms ('signs or symptoms of GCA') and symptoms of PMR. Fever was infrequently reported across all of the treatment groups. More than half of the placebo treated patients had an elevated ESR attributed to GCA at some point during the study (60.0% in the PBO + 26 week group and 56.9% in the PBO + 52 week group) compared to 6.0% and 14.3% in the TCZ QW and TCZ Q2W groups, respectively.

A summary of signs and symptoms that were only present at the time of flare (as determined by the investigator) showed a similar profile across treatment groups. The most commonly reported symptoms at time of flare were cranial signs and symptoms of GCA and symptoms of PMR. Very few patients had fever at the time of flare in any of the treatment groups. Visual complications were present at Baseline in a small number of patients in each of the treatment groups. Visual complications that occurred after the baseline visit, whether or not associated with disease flare, were reported throughout the study. Blurred vision was the most commonly reported symptom that occurred after the baseline visit. There were no new reports of permanent unilateral or bilateral vision loss during the study**.** New-onset visual complications at the time of flare were reported in the PBO + 26 week (4 patients), PBO + 52 week (5 patients) and TCZ Q2W (2 patients) groups, while there were no events in the TCZ QW group.

The cumulative prednisone dose to Week 52 was statistically significantly lower in both the TCZ QW and TCZ Q2W treatment groups when compared to placebo in combination with a 26 week prednisone taper period. Similar 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. A plot of the cumulative prednisone dose over time based on observed data (Figure 9) shows that the curves of median cumulative prednisone dose were similar in the TCZ and placebo treatment groups up to approximately Week 22 (which corresponds to the time at which the blinded prednisone taper approaches 0 mg/day for these groups between Weeks 21 and 27, depending on starting prednisone dose), after which the curves for the TCZ QW and TCZ Q2W treatment groups start to plateau reflecting the fact that patients in these treatment groups received little additional prednisone, as per the study design and owing to the lower proportion of patients experiencing flare. In the placebo groups, the median cumulative prednisone dose continued to increase throughout the study with the highest median cumulative prednisone dose being observed in the PBO + 52 week group, partly due to study design but also as a result of the number of escape patients receiving increased steroid doses.

Figure 9: Plot and summary of cumulative prednisone dose to Week 52 (ITT)



For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) will be assumed to be the minimum dose tablet(s) available from that pack.
Patients who received increased prednisone due to entering escape therapy will be included in their original treatment group.
Patients who withdraw are excluded from the summaries for subsequent visits.
Prednisone records are reported up to study day 364. Week 0 to Week 51 includes the 52 weeks of Part 1 prednisone exposure.

Exploratory efficacy endpoints: The mean annualised GCA relapse rate (which accounts for multiple flares in one patient) was highest in the PBO + 26 week (1.74/year) and PBO + 52 week (1.30/year) groups with lower relapse rates of 0.41/year in the TCZ QW group and 0.67/year in the TCZ Q2W group.

Response rates over time declined at a steady rate across all treatment groups with the largest decline between visits in response rates seen in the PBO + 26 week group (-12%) and the TCZ Q2W group (-10.3%), both at Week 24, which is in line with approximately when the prednisone taper would have approached 0 mg/day in these groups. In the TCZ QW and PBO + 52 week groups, the largest declines were seen at Week 20 (-5.0%) and Week 48 (-5.8%), respectively. The proportion of patients who had achieved remission (without receiving escape prednisone) at Week 12 was 83.0% in the TCZ QW group, 81.6% in the TCZ Q2W group, 49.0% in the PBO + 52 week group and 42.0% in the PBO + 26 week group. This treatment difference was maintained throughout the duration of the study to Week 52, at which point the proportion of patients in sustained remission was 56.0% in the TCZ QW group, 53.1% in the TCZ Q2W group, 17.6% in the PBO + 52 week group and 14.0% in the PBO + 26 week group.

A lower proportion of patients in the TCZ treatment groups remained on active prednisone to Week 52 compared with the placebo groups. By Week 51 glucocorticoids were being received by 18/100 (18%) of patients in the TCZ QW group and 10/49 (20%) of patients in the TCZ Q2W group compared with 28/50 (56%) of patients in the PBO + 26 week group and 27/51 (53%) of patients in the PBO + 52 week group.

Escape therapy: A lower proportion of patients stopped the protocol defined prednisone taper and moved onto treatment with escape prednisone in the TCZ QW (23.0%) and TCZ Q2W (32.7%) groups compared with patients in the PBO + 52 week (54.9%) and PBO + 26 week (74.0%) groups. Median prednisone starting dose for the escape patient population was 30.0 mg in each of the TCZ QW, TCZ Q2W and PBO + 26 week groups and 37.5 mg in the PBO + 52 week group. There was no consistent pattern to the time of initiation of escape therapy.

Patient reported outcomes: 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 week group (p = 0.0059) and PBO + 52 week 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.

The change from Baseline to Week 52 for the SF-36 Mental Component Score showed a numeric improvement in all treatment groups (placebo and TCZ), although none of the comparisons between TCZ and placebo met the level of statistical significance of 0.01.

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. Only the difference observed in the TCZ QW group compared to the PBO + 52 week group was statistically significant at the 0.01 significance level (p = 0.0024). Change from Baseline scores for the 8 individual domains comprising the SF-36 component scores (Mental Health, Vitality, Social Functioning, Role-Emotional, General Health, Bodily Pain, Physical Functioning and Role-Physical) were consistent with the total MCS and PCS change from Baseline scores, with both TCZ arms showing numeric improvement. No individual domain change score appeared to influence the overall component scores for any treatment arm.

Numerically higher mean changes from Baseline in the FACIT Fatigue scores at Week 52 were observed in the TCZ QW (5.61 ± 10.12) and TCZ Q2W (1.81 ± 8.84) treatment groups compared with either the PBO + 26 week group (0.26 ± 10.70) or PBO + 52 week group (-1.63 ± 6.75). There was no notable deterioration in mean EQ-5D scores in any treatment group over time. Mean (SD) change from Baseline scores at Week 52 were 0.10 (0.198) in the TCZ QW group, 0.05 (0.215) in the TCZ Q2W group, 0.07 (0.293) in the PBO + 26 week group and -0.02 (0.159) in the PBO + 52 week group. Higher scores signal improvement in both FACIT-Fatigue and EQ5D.

8.2.1.14. *Results from OL phase (Part 2 of Study WA28119)*

Comment: The 104 week open-label period (Part 2) is still ongoing and results were not provided in the CSR for pivotal Study WA28119. The objective of Part 2 of the study was 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. The following information was provided in the clinical overview but could not be confirmed by the evaluators.

'*Patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open-label extension phase (Part 2) of the study. Preliminary data from 45 patients that met the primary endpoint in Part 1 and were followed for at least an additional 48 weeks revealed that a higher proportion of patients that*

previously received TCZ Q2W experienced a GCA flare (73%, 8/11) in Part 2 compared to those who previously received TCZ QW during Part 1 (33%, 8/24). This is consistent with the concept that the TCZ QW regimen may be more effective at suppressing disease activity than the TCZ Q2W dose.'

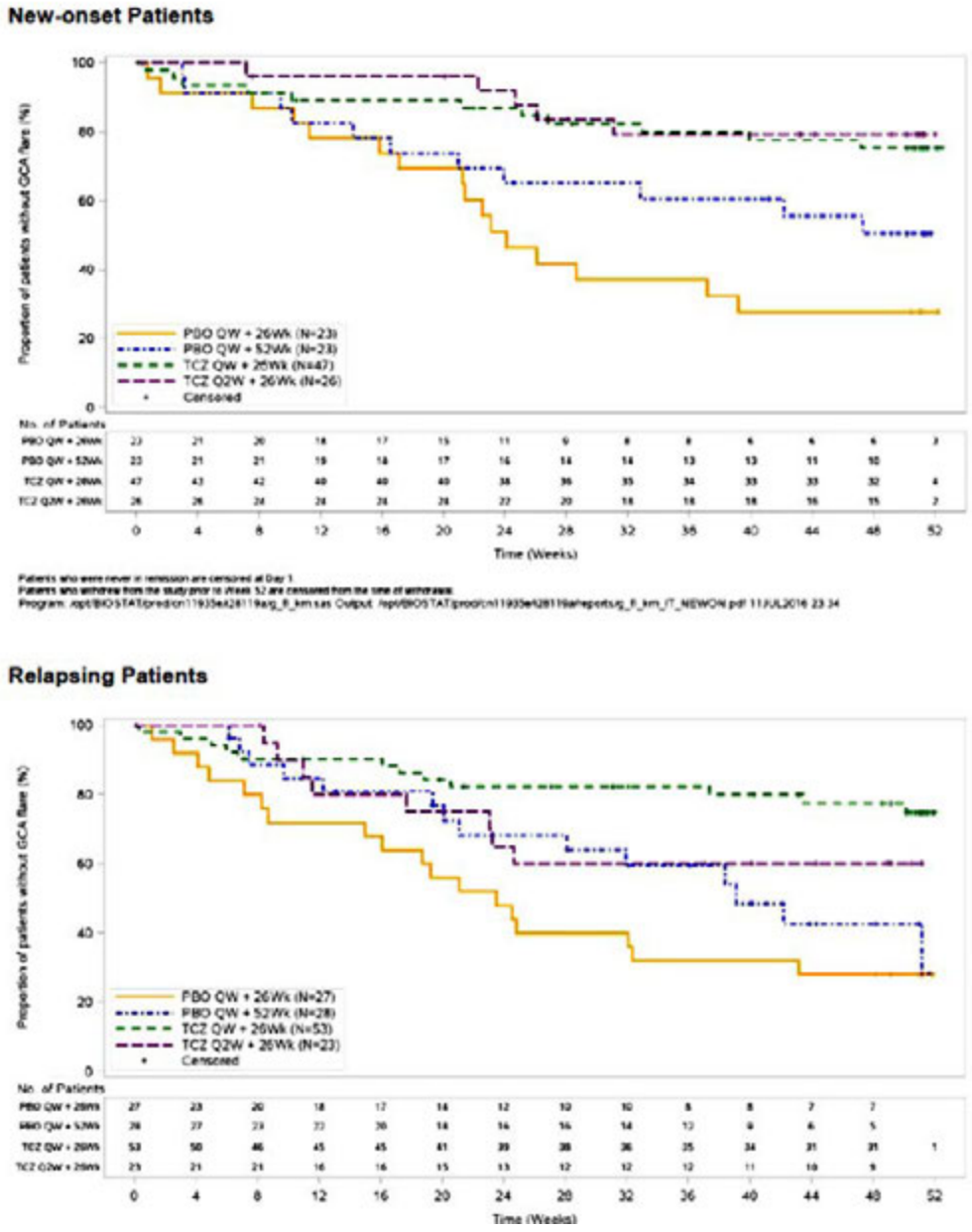
8.2.1.15. *Subgroup analysis*

By Disease onset at Baseline: The actual enrolment of patients with relapsing GCA was 53%, while 47% of patients enrolled had new-onset GCA. There was a balanced distribution of new-onset or relapsing patients in each of the treatment groups. The proportion of patients achieving sustained remission at Week 52 was numerically higher in patients with new-onset GCA disease at Baseline compared with relapsing GCA patients. The difference in the proportion of patients achieving sustained remission at Week 52 between the TCZ groups and the PBO + 52 week group was similar among new-onset GCA patients and relapsing GCA patients. However, the difference between the TCZ groups and PBO + 26 week group was greater in relapsing GCA patients than in new-onset GCA patients mainly due to fewer relapsing patients in the PBO + 26 week group achieving sustained remission at Week 52. In both new-onset and relapsing GCA patient subgroups, the difference in the proportion of patients with sustained remission was numerically higher in the TCZ QW group compared with the TCZ Q2W group and slightly more pronounced in the relapsing patient subgroup.

Comment: The above information was provided in the CSR but details regarding actual sustained remission rates in the new onset and relapsing GCA patients to support the above statements was not provided in the CSR. The sponsors have been requested to provide this information (refer Clinical questions below).

In new-onset GCA patients, the median time to GCA disease flare following clinical remission was 169 days in the PBO + 26 week group but was not calculable in the PBO +52 week, TCZ QW and TCZ Q2W groups, due to the fact that fewer than 50% of the new onset patients in these groups (48%, 23% and 19%, respectively) had experienced a flare by Week 52. The hazard ratios (HRs) versus placebo in combination with a 26 week prednisone taper were 0.25 (99% CI: 0.09 to 0.70) for the TCZ QW group and 0.20 (99% CI: 0.05 to 0.76) for the TCZ Q2W group indicating a lower risk of flare in patients in both TCZ dose groups. There was a clear separation between the TCZ treatment groups and the PBO groups with the shortest median time to GCA flare observed in the PBO + 26 week group. There was a high degree of overlap between the TCZ QW and TCZ Q2W dose groups (Figure 10). In relapsing patients, median time to GCA disease flare following clinical remission was 165 days in the PBO + 26 week group and 274 days in the PBO + 52 week but was not calculable in the TCZ QW and TCZ Q2W groups due to the fact that fewer than 50% of the patients in these groups (23% and 35%, respectively) had experienced a flare by Week 52. The hazard ratios (HRs) versus placebo in combination with a 26 week prednisone taper were 0.23 (99% CI: 0.09 to 0.61) for the TCZ QW group and 0.42 (99% CI: 0.14 to 1.28) for the TCZ Q2W group, indicating a lower risk of flare for patients in the TCZ groups versus placebo. There was a clear separation between the TCZ QW treatment group and the TCZ Q2W and PBO groups with considerable overlap between the TCZ Q2W and PBO + 52 week curves until approximately Week 38 of the study (Figure 10).

Figure 10: Kaplan-Meier Plot of Time to First GCA disease flare by disease status at Baseline (ITT Population)



Median actual cumulative prednisone dose to Week 52 was lower in both TCZ treatment groups in relapsing patients compared to new-onset patients. However, in both new-onset and relapsing patient subgroups, a lower median cumulative glucocorticoid dose to Week 52 was observed in both TCZ QW groups compared to placebo in combination with both a 26 week and 52 week prednisone taper, with a greater numerical difference observed for the TCZ QW group (Table 13).

Table 13: Cumulative Glucocorticoid Dose by Disease Status at Baseline (ITT Population).

	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
New-onset (n)	23	23	47	26
Mean	3632.11	4136.83	2406.67	2712.29
SD	2212.91	2055.62	1341.88	1850.21
Median (mg)	3068.00	3817.50	1942.00	2202.00
min-max	1125.0 - 9777.5	2017.5 - 10275.0	630.0 – 6602.5	982.0 – 9912.5
95% CI	(2262.0, 4289.0)	(2577.5, 4584.5)	(1822.0, 2519.0)	(1815.5, 3079.0)
Relapsing (n)	27	28	53	23
Mean	3878.56	4250.06	1823.96	2147.11
SD	1880.44	2504.68	1100.85	1793.86
Median (mg)	3860.50	3785.50	1385.00	1568.00
min-max	932 – 8043.5	822.5 – 10697.5	658.0 – 5912.0	295.0 – 8410.0
95% CI	(2678.0, 5116.5)	(2222.5, 5372.5)	(1127.0, 1862.0)	(1114.5, 2239.5)

Van Elteren's test was used to calculate p-values. Analysis was stratified by starting prednisone dose (≤ 30mg/day, >30mg/day).

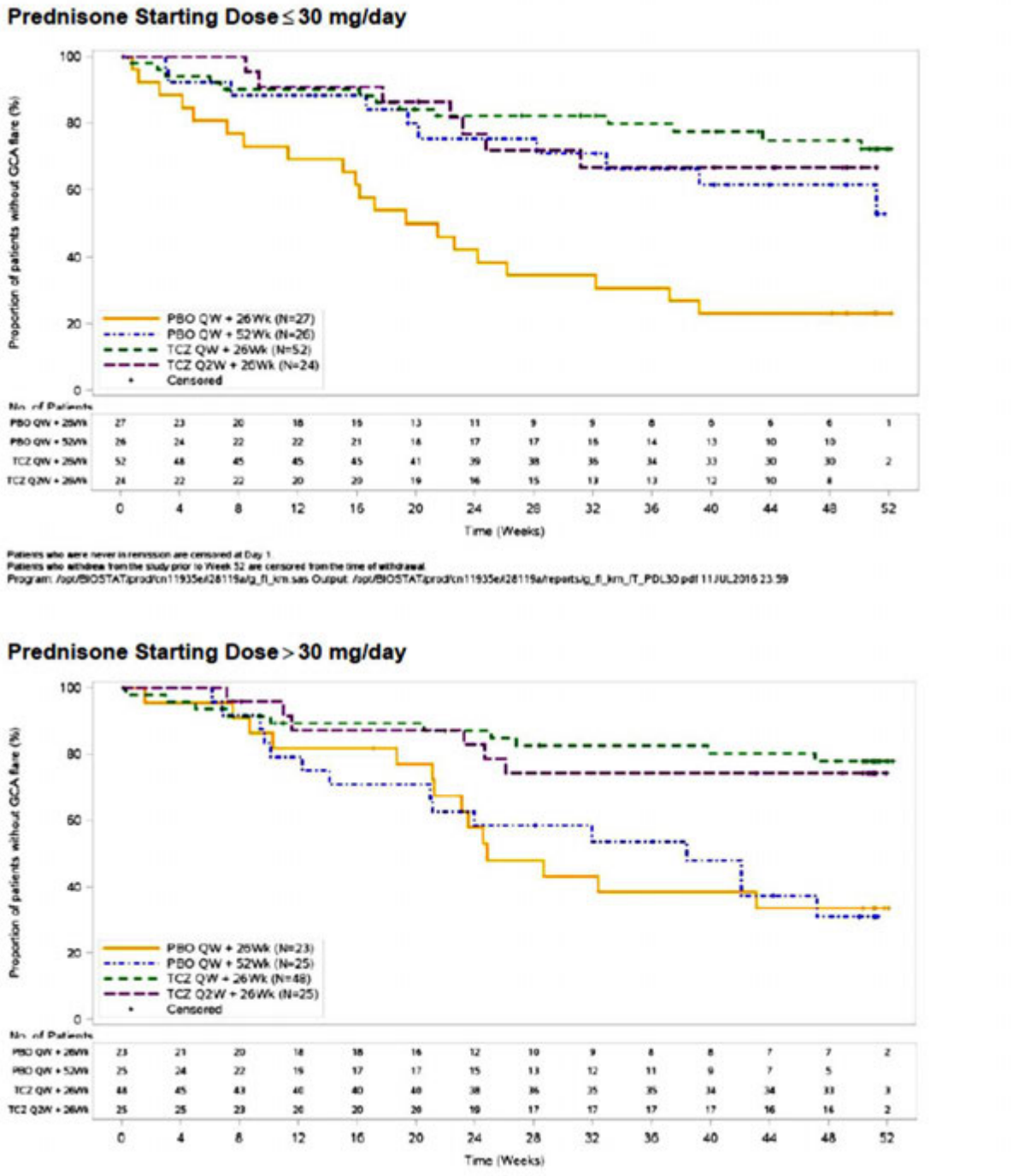
For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) were assumed to be the minimum dose tablet(s) available from that pack. Patients who received increased prednisone due to entering escape therapy were included in their original treatment group.

Actual cumulative dose is based on actual records of prednisone taken and includes all escape therapy and commercial prednisone as well as taper prednisone.

By Starting Prednisone dose: The proportion of patients achieving sustained remission at Week 52 was numerically higher in patients with a starting prednisone dose > 30 mg/day compared with patients with a prednisone starting dose ≤ 30 mg/day. However, there was no obvious impact of starting prednisone dose on the difference between the TCZ and the placebo groups in the proportion of patients achieving sustained remission at Week 52.

In patients with a starting prednisone dose ≤ 30 mg/day, the median time to GCA disease flare following clinical remission was 142.5 days in the PBO + 26 week group but was not calculable in the PBO + 52 wk, TCZ QW and TCZ Q2W groups, as fewer than 50% of the patients in these groups (39%, 25% and 29%, respectively) had experienced a GCA disease flare by Week 52. The hazard ratios (HRs) versus placebo in combination with a 26 week prednisone taper were 0.21 (99% CI: 0.08 to 0.54) for the TCZ QW group and 0.28 (99% CI: 0.09 to 0.86) for the TCZ Q2W group indicating a lower risk of flare in patients in both TCZ dose groups. There was a clear separation between the TCZ QW treatment group and the TCZ Q2W and PBO groups from approximately Week 24 onwards, with the PBO + 26 week group showing clear separation from the other curves from start of treatment. Notably, there is considerable overlap between the TCZ Q2W and PBO + 52 week curves (Figure 11). In patients with a starting prednisone dose > 30 mg/day, median time to GCA disease flare following clinical remission was 174 days in the PBO + 26 week group and 269 days in the PBO + 52 week group, while medians were not calculable in the TCZ QW and TCZ Q2W groups (only 21% and 24% of patients in these groups, respectively, had flared by Week 52). The hazard ratios (HRs) versus placebo in combination with a 26 week prednisone taper were 0.25 (99% CI: 0.09 to 0.74) for the TCZ QW group and 0.30 (99% CI: 0.08 to 1.05) for the TCZ Q2W group, indicating a lower risk of flare for patients in the TCZ groups versus placebo. The Kaplan-Meier plot shows a clear separation between the TCZ treatment groups and the PBO groups as early as Week 12 while there is a high degree of overlap between the TCZ QW and TCZ Q2W dose groups. At approximately Week 22 (mid-point of the study), the TCZ curves start to separate with an apparent longer time to flare observed in the TCZ QW group (Figure 11).

Figure 11: Kaplan-Meier Plot of Time to First GCA disease flare by starting prednisone dose (≤ 30 mg/day, >30 mg/day) (ITT Population).



By previous history of remission: In relapsing patients who had a history of GCA disease remission, sustained remission at Week 52 was achieved in 51% (19/37) of patients in the TCZ QW group and 38% (6/16) of patients in the TCZ Q2W group compared with 18% (3/17) of patients in the PBO + 52 week group and 0% (0/18) patients in the PBO + 26 week group. In relapsing patients who had never been in remission despite glucocorticoid treatment, sustained remission at Week 52 was achieved in 56% (9/16) and 71% (5/7) of patients in the TCZ QW and TCZ Q2W groups, respectively, compared with 9% (1/11) of patients in the PBO + 52 week group and 22% (2/9) of patients in the PBO + 26 week group. However, interpretation of these results was limited by small number of patients as this subgroup contains less than 20% of the overall study population.

By Imaging or biopsy at diagnosis: In the subgroup of patients with large vessel involvement confirmed by imaging techniques (all patients with a positive diagnosis of GCA by imaging), the proportion of patients achieving sustained remission at Week 52 whilst adhering to the protocol defined prednisone regimen was 60% (30/50) in the TCZ QW group and 57% (13/23) in the TCZ Q2W group compared with 21% (4/19) in the PBO + 26 week group and 17% (4/23) in the PBO + 52 week group. Analysis of the proportion of patients achieving sustained remission at Week 52 whilst adhering to the protocol-defined prednisone regimen for the subgroup diagnosed by a positive temporal artery biopsy only (that is, without imaging) showed results that were consistent with the overall ITT population by way of sustained remission at Week 52 being achieved in 52% (26/50) of patients in the TCZ QW group and 50% (13/26) of patients in the TCZ Q2W group compared with 10% (3/31) of patients in the PBO + 26 week group and 19% (5/27) of patients in the PBO + 52 week group.

By GCA Diagnosis based on 1990 ACR Criteria for the Classification of GCA: An analysis was performed of the proportion of patients achieving sustained remission at Week 52 whilst adhering to the protocol-defined prednisone regimen for the subgroup of patients that met the 1990 ACR classification criteria for GCA, defined as having at least 3 out of the following 5 symptoms: aged ≥ 50 years, ESR ≥ 50 mm/hour, new-onset localised headache, temporal artery abnormality, abnormal artery biopsy (that is, positive TAB). The majority of patients in the TCZ QW (79%; 79/100), TCZ Q2W (80%; 39/49), PBO + 26 week (76%; 38/50) and PBO + 52 week (78%; 40/51) groups met the 1990 ACR entry criteria. Results for patients meeting the 1990 ACR classification criteria were consistent with the overall ITT population. Sustained remission at Week 52 was achieved in 58% (46/79) of patients in the TCZ QW group and 56% (22/39) of patients in the TCZ Q2W group compared with 18% (7/40) of patients in the PBO + 52 week group and 11% (4/38) of patients in the PBO + 26 week group. In patients who did not meet the ACR 1990 entry criteria, a higher proportion in the TCZ QW (48%; 10/21 patients) and TCZ Q2W (40%; 4/10 patients) groups achieved sustained remission at Week 52 compared with the PBO + 52 week (18%; 2/11 patients) and PBO + 26 week (25%; 3/12) groups. However, results should be treated with caution due to the limited sample size.

By GCA Signs and Symptoms at the Time of Diagnosis: Subgroup analysis of the proportion of patients achieving sustained remission at Week 52 whilst adhering to the protocol-defined prednisone regimen by GCA signs and symptoms at the time of diagnosis showed that, consistent with the ITT analysis, a higher proportion of patients in the TCZ groups achieved sustained remission at Week 52 compared with the placebo groups. In patients with cranial symptoms only, patients with PMR symptoms only and in patients with both cranial symptoms and symptoms of PMR, results were consistent across the treatment groups.

8.2.1.16. *Evaluator commentary*

Study WA28119 was a well-conducted study in 251 patients with GCA. The majority of patients enrolled in this pivotal study were Caucasian females with 2-third of patients aged ≥ 65 years representing the epidemiological profile of GCA patients in the wider population. The study included patients with both relapsing and new-onset GCA disease. Furthermore, revised diagnostic criteria consistent with current clinical practice were used in order to include patients with large-vessel GCA. The study was well-designed with use of a stringent and clinically meaningful efficacy endpoint of sustained remission (no GCA flare) for 40 weeks and off glucocorticoids for 6 months. The use of 2 double blind, variable dose and variable duration prednisone tapering regimens represented current clinical practice.

The study met its primary and key secondary endpoints demonstrating that tocilizumab 162 mg SC QW and Q2W regimens are effective at maintaining steroid-free remission in patients with GCA. Superiority of both TCZ regimens over placebo in combination with a 26 week prednisone taper regimen was demonstrated with respect to the proportion of patients in sustained remission at Week 52, following induction and adherence to the protocol-defined prednisone taper regimen. Sensitivity analyses of the primary endpoint (tipping point analysis, analysis

excluding the requirement for normalised CRP < 1 mg/dL from the definition of remission, analysis of completers adhering to blinded TCZ/placebo study medication, analysis irrespective of adherence to prednisone taper regimen) were consistent with the primary analysis for both TCZ dose groups, demonstrating the robustness of the primary analysis. Non-inferiority of both TCZ regimens over placebo in combination with a 52 week prednisone taper was established with respect to the proportion of patients in sustained remission at Week 52, following induction and adherence to the protocol defined prednisone taper regimen. Furthermore, superiority of the TCZ groups compared to the placebo group in combination with a 52 week prednisone taper was demonstrated.

Both TCZ regimens were associated with fewer GCA flares compared with placebo with the reduction in risk of flare reaching statistical significance for the TCZ QW group. Average cumulative steroid doses were significantly lower in the TCZ groups compared to the placebo groups. This reduction in steroid exposure is considered to be clinically meaningful with respect to decreasing the toxicity burden of high dose steroid exposure.

Health Related Quality of Life, assessed by PRO measures (SF-36, patient's global assessment VAS and FACIT-Fatigue) consistently demonstrated trends towards improvement in both TCZ treatment groups.

With respect to the relative efficacy of QW and Q2W SC tocilizumab regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW tocilizumab. Moreover, consistent trends favouring QW over Q2W tocilizumab were seen for several additional endpoints and subgroup analyses.

Overall this study provided adequate evidence to support use of the proposed weekly treatment with SC TCZ 162 mg for treatment of adults with active GCA.

8.3. Other efficacy studies

8.3.1. Study ML25676 (Villiger, 2016)

Comment: It is important to note that the original CSR for this study was not provided and only the literature reference was provided in the submitted dossier.

The sponsor-supported investigator-initiated, randomised, double blind, placebo controlled, Phase II Study ML25676, investigated 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 randomised (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 design and patient disposition is summarised in Figure 12.

Between 3 March 2012 and 9 September 2014, 20 patients were randomly assigned to receive tocilizumab and prednisolone, and 10 patients to receive placebo and glucocorticoid; 16 (80%) and 7 (70%) patients, respectively, had new-onset giant cell arteritis (see Table 14). 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)) (Table 15). 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; relapse-free survival was achieved in 17 (85%) patients in the tocilizumab group and 2 (20%) in the placebo group by Week 52 (risk difference 65%, 95% CI 36–94; p = 0·0010). The mean survival-time difference to stop glucocorticoids was 12 weeks in favour of tocilizumab (95% CI 7, 17; p < 0.0001), leading to a cumulative prednisolone dose of 43 mg/kg in the

tocilizumab group versus 110 mg/kg in the placebo group (p = 0·0005) after 52 weeks (Figure 13).

Figure 12: Study ML24676 (Villiger, 2016): Study design and patient disposition

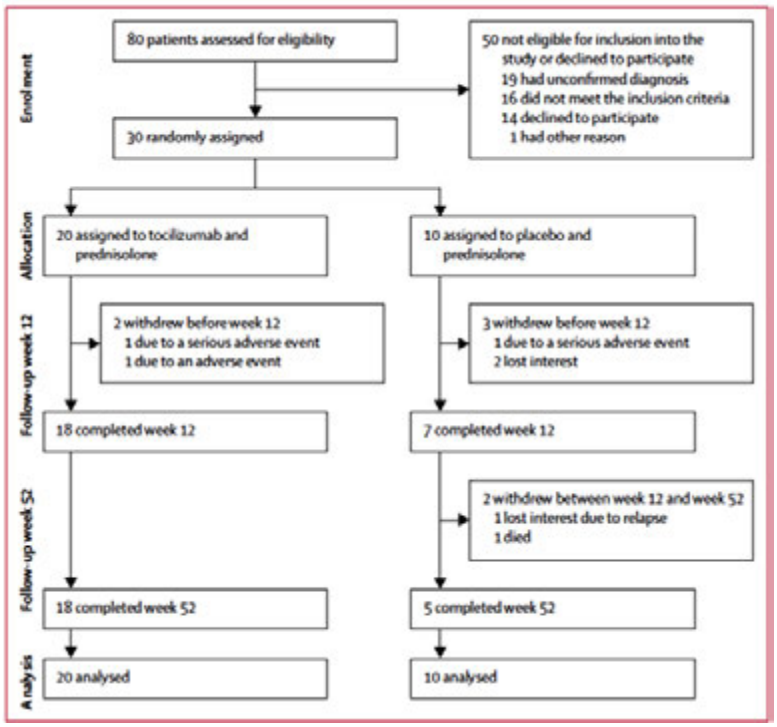


Table 14: Study ML24676 (Villiger, 2016): Baseline characteristics

	Tocilizumab plus prednisolone (N=20)	Placebo plus prednisolone (N=10)
Women	13 (65)	8 (80)
Age (years)	71·3 (8·9)	68·8 (16·9)
BMI (kg/m²)	23·6 (3·0)	27·9 (3·7)
New-onset giant cell arteritis	16 (80)	7 (70)
Biopsy of the temporal artery		
Normal	5 (25%)	0
Abnormal	13 (65%)	8 (80%)
Not done	2 (10%)	2 (20%)
Thoracoabdominal MR angiography		
Normal	9 (45%)	2 (20%)
Abnormal	11 (55%)	6 (60%)
Not done	0	2 (20%)
Symptoms and signs of giant cell arteritis		
Fever	1 (5%)	1 (10%)
Weight loss	6 (30%)	3 (30%)
Night sweats	3 (15%)	2 (20%)
Headache	13 (65%)	5 (50%)
Scalp tenderness	9 (45%)	1 (10%)
Claudication of tongue	2 (10%)	0
Masseter muscle claudication	11 (55%)	4 (40%)
Claudication of upper limbs	4 (20%)	2 (20%)
Claudication of lower limbs	0	2 (20%)
Visual impairment	5 (25%)	2 (20%)
Blood pressure (mmHg)		
Systolic right arm	130·6 (18·0)	137·7 (16·4)
Diastolic right arm	74·3 (11·8)	77·7 (15·2)
Systolic left arm	131·3 (16·3)	136·9 (13·0)
Diastolic left arm	75·1 (11·5)	82·8 (8·5)
Erythrocyte sedimentation rate (mm/h)		
At screening	69·0 (45·5–80·0)	40·0 (27·3–68·8)
At remission	5·0 (4·3–7·8)	6·5 (3·5–12·5)
C-reactive protein (mg/L)		
At screening	25·5 (16·8–50·3)	39·0 (23·5–64·3)
At remission	0·0	0·0

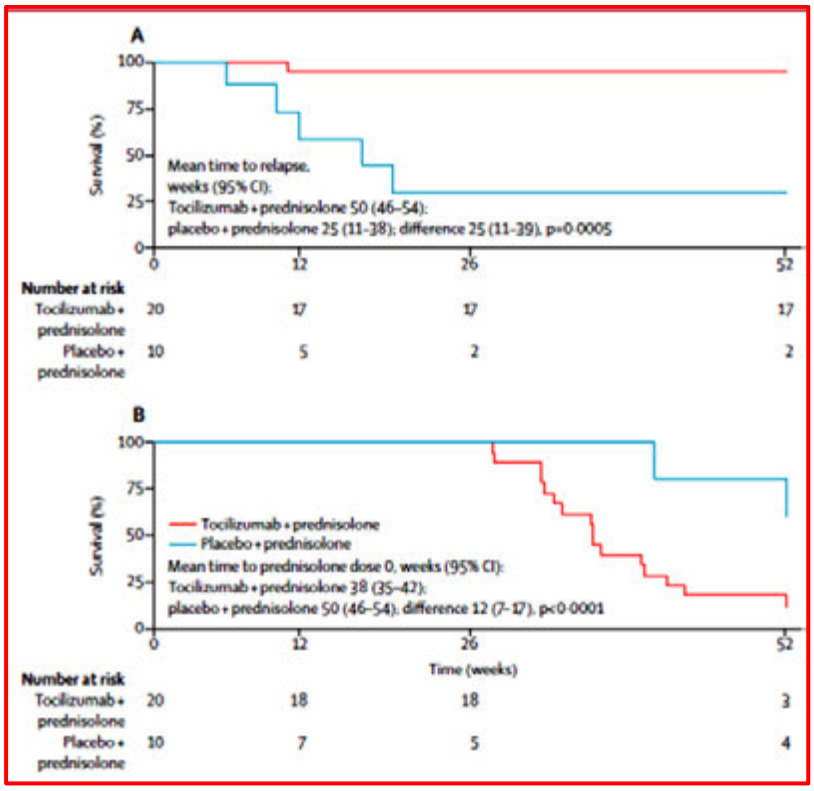
Data are n (%), mean (SD), or median (IQR).

Table 15: Study ML24676 (Villiger, 2016): Treatment effects on primary and secondary endpoints:

	Tocilizumab plus prednisolone (N=20)	Placebo plus prednisolone (N=10)	Risk difference (95% CI)	p value
Endpoints				
Complete remissions				
After 12 weeks	17 (85%)	4 (40%)	45% (11 to 79)	0·0301
After 52 weeks	17 (85%)	2 (20%)	65% (36 to 94)	0·0010
Patients whose prednisolone dose tapered to 0 mg per day	16 (80%)	2 (20%)	60% (30 to 90)	0·0041
Cumulative prednisolone dose (mg/kg)				
After 12 weeks	34 (32 to 35)	36 (34 to 39)	..	0·0477
After 26 weeks	41 (39 to 46)	66 (52 to 75)	..	0·0015
After 52 weeks	43 (39 to 52)	110 (88 to 150)	..	0·0005
Patients with any adverse event	15 (75%)	7 (70%)	5% (−29 to 39)	1·00
Patients with a serious adverse event	7 (35%)	5 (50%)	−15% (−52 to 22)	0·46
First relapse*				
Timepoint of first relapse (weeks)	11·0	12·0 (10·1 to 17·1)	..	0·77
Prednisolone dose at first relapse (mg/kg per day)	0·11	0·10 (0·09 to 0·17)	..	0·77
Erythrocyte sedimentation rate at first relapse (mm/h)	2·00	20·0 (10·0 to 30·0)	..	0·14
C-reactive protein concentration at first relapse (mg/L)	3·00	16·0 (11·0 to 25·0)	..	0·23

Data are n (%) or median (IQR) unless stated otherwise. *One patient in the tocilizumab group and five in the placebo group had first relapse.

Figure 13: Study ML24676 (Villiger, 2016): Kaplan Meier curve for relapse free survival through to Week 52 (A) and the time to taper down prednisolone to 0 mg per day (B).



A recent abstract further reported longer-term outcomes beyond Week 52 at which point TCZ medication was stopped (Adler et al. 2016). At Week 52 all of the 20 TCZ treated patients were in remission, 18 of which had discontinued concomitant glucocorticoid therapy. Patients were followed for a median time of an additional 12.5 months (range: 3- 32). Following the last infusion of TCZ at Week 52, more than half of the patients (11/20) experienced GCA relapse within a median time of 5 months (range: 2-14). Six of the 11 patients that relapsed were re-treated with monthly TCZ 8 mg/kg IV. TCZ retreatment was stopped after 4 and 6 months in 2/6 patients following lasting remission. In 1/6 patients, TCZ was stopped after 2 months following remission, but had to be re-introduced 6 month later due to a second relapse.

8.3.2. Evaluator commentary on other efficacy studies

Study ML25676 (Villiger, 2016) was the first randomised, placebo controlled trial of tocilizumab (8mg IV every 4 weeks for 1 year) in patients with giant cell arteritis and the results show the drug's effectiveness in inducing remission and preventing relapse. Glucocorticoids could be rapidly tapered and discontinued by 36 weeks after the initiation of tocilizumab treatment.

8.4. Analyses performed across trials: pooled and meta analyses

Not applicable.

8.5. Evaluator's conclusions on clinical efficacy

Study WA28119 was a well-conducted pivotal Phase III, placebo controlled (for 12 months), randomised, multicentre study in 251 patients with GCA. Majority of patients enrolled in this pivotal study were Caucasian females with 2-third of patients aged ≥ 65 years which represented the epidemiological profile of GCA patients in the wider population. The study included patients with both relapsing and new-onset GCA disease. Furthermore, revised

diagnostic criteria consistent with current clinical practice were used in order to include patients with large-vessel GCA. The study was well-designed with use of a stringent and clinically meaningful efficacy endpoint of sustained remission (no GCA flare) for 40 weeks and off glucocorticoids for 6 months. The use of 2 double blind, variable dose and variable duration prednisone tapering regimens (over 26 and 52 weeks) were representative of current clinical practice. 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 156 weeks. Clinical conduct of Part 1 of the study is complete and the Part 2 extension is currently ongoing.

The study met its primary and key secondary endpoints demonstrating that tocilizumab 162 mg SC QW and Q2W regimens are effective at maintaining steroid-free remission in patients with GCA. Following induction and adherence to the protocol-defined prednisone taper regimen, the proportion of patients in sustained remission at Week 52 was statistically and clinically significantly greater in both the TCA QW (56%) and Q2W (53%) groups compared with the placebo (14%) group. Sensitivity analyses of the primary endpoint confirmed the robustness of the primary analysis. Non-inferiority and subsequently superiority of both TCZ regimens over placebo in combination with a 52 week prednisone taper was established with respect to the proportion of patients in sustained remission at Week 52, following induction and adherence to the protocol defined prednisone taper regimen.

Both TCZ regimens were associated with fewer GCA flares compared with placebo with the reduction in risk of flare. Average cumulative steroid doses were significantly lower in the TCZ groups compared to the placebo groups. By Week 51, only 18-20% of patients in both TCZ groups remained on active prednisone compared with 53-56% in the placebo groups. The glucocorticoid sparing effect of TCZ in Study WA28119 was both highly statistically and clinically meaningful. The median cumulative dose of prednisone at Week 52 (including all taper prednisone and escape therapy) received by the PBO + 52 week group was more than double the cumulative doses received by the TCZ QW or Q2W groups (PBO + 52 week 3817.5 mg; TCZ QW and Q2W 1862.0 mg). Moreover, owing to the additional escape prednisone required to control disease flares, patients in the PBO + 26 week group received almost twice the cumulative glucocorticoid exposure (3296.0 mg) than either TCZ group. This reduction in steroid exposure is clinically meaningful especially due to the toxicity associated with high dose steroid exposure.

Health Related Quality of Life, assessed by PRO measures (SF-36, patient's global assessment VAS and FACIT-Fatigue) consistently demonstrated trends towards improvement in both TCZ treatment groups.

Efficacy of TCZ 162 mg SC every week (QW) or every 2 weeks (Q2W) was observed in all subgroups based on disease onset (new onset and relapsing patients), starting prednisone dose (≤ or > 30 mg/day), by previous history of remission, by GCA diagnosis by imaging or biopsy, by GCA diagnosis based on 1990 ACR criteria or by GCA signs and symptoms at diagnosis.

With respect to the relative efficacy of QW and Q2W SC tocilizumab regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW tocilizumab, especially in the sensitivity analysis (refer section Pivotal study above). Moreover, consistent trends favouring QW over Q2W tocilizumab were seen for several additional endpoints and subgroup analyses. In both new-onset and relapsing GCA patient subgroups, the difference in the proportion of patients with sustained remission was numerically higher in the TCZ QW group compared with the TCZ Q2W group and slightly more pronounced in the relapsing patient subgroup. This is especially clinically relevant as relapsing patients represents those who have already been exposed to high dose and long duration glucocorticoid regimens and present special challenges for physicians who have little choice but to re-start or to increase the dose of glucocorticoid therapy as there are currently no proven glucocorticoid-sparing therapies.

Supportive evidence of efficacy was provided by the randomised, double blind, placebo controlled, Phase II Study ML25676 (Villiger, 2016). This was the first randomised controlled trial of TCZ in 30 patients with new onset or relapsing GCA disease randomised (2:1) to receive 8 mg/kg IV TCZ every 4 weeks (Q4W) or placebo over 1 year. Results from this study showed the efficacy of TCZ in inducing remission and preventing relapse. Glucocorticoids could be rapidly tapered and discontinued by 36 weeks after the initiation of TCZ treatment.

The evidence for efficacy and safety of GCA beyond 1 year was not provided in this submission. In Study WA28119, patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open-label extension phase (Part 2) of the study. GCA is usually associated with common occurrence of disease flares during glucocorticoid dose tapering or discontinuation. Therefore, it is highly likely that many patients with GCA will require treatment beyond 52 weeks in routine clinical practice. Results from the OL phase were not provided in the CSR for Study WA28119, although the Clinical overview mentions that preliminary data from 45 patients that met the primary endpoint in Part 1 and were followed for at least an additional 48 weeks suggest that a substantial subset of GCA patients are likely to experience clinical disease flares within a year or so of stopping TCZ; the proportion of patients that previously received TCZ Q2W experienced a GCA flare (73%, 8/11) in Part 2 compared to those who previously received TCZ QW during Part 1 (33%, 8/24). Study ML25676 (Villiger, 2016) also showed relapse in over 50% of patients following discontinuation of TCZ (8mg IV every 4 weeks) after a 52 week treatment course (Adler et al. 2016). In clinical practice, some patients may be successful in sustaining disease remission off therapy, yet others may require re-treatment and ongoing TCZ treatment in order to maintain disease control. The evaluators feel that the choice to continue treatment beyond 52 weeks should be guided by disease activity, physician assessments, patient choice and emerging data including but not limited to long-term, OL data from pivotal Study WA28119.

9. Clinical safety

9.1. Studies providing evaluable safety data

The main clinical safety data was provided by the pivotal Phase III Trial WA28119 (GiACTA), which evaluated the efficacy and safety of subcutaneous (SC) TCZ treatment compared with placebo in 251 patients with GCA (clinical cutoff date 11 April 2016). Other supportive evidence was provided by the Phase II Study ML25676 which evaluated intravenous (IV) TCZ in patients with newly diagnosed or relapsing GCA.

9.2. Pivotal and/or main efficacy studies

9.2.1. Study WA28119

Safety assessments included AEs, standard laboratory assessments, physical examination, vital signs and immunogenicity. Events related to GCA were not reported as AEs but were captured in the Case Report Form (CRF) as signs and symptoms of GCA flare, unless considered serious events related to GCA, in which case they were reported as serious adverse events (SAEs). AEs were graded by intensity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 grading system and by relationship to study treatment (unrelated or related) and were to be followed until they had returned to baseline or stabilised. AEs were tabulated by body system and preferred term within each body system and presented in order of descending frequency. A pre-existing medical condition[18] was

[18] A pre-existing medical condition was the one that presented at the screening visit for this study. Such conditions were recorded on the General Medical History and Baseline Conditions electronic CRF.

recorded as an AE only if the frequency, severity or character of the condition worsened during the study. Verbatim terms reported were coded to preferred terms using the Medical dictionary for Regulatory Activities (MedDRA), v19.0 terminology for AEs and diseases. SAEs and AEs leading to withdrawal, dose modification, or interruption were summarised separately. Multiple reports of a particular event for a patient were counted only once in summaries of AEs, using the most severe intensity and strongest relationship to treatment reported for the event. In addition, a patient was included only once in the total number of patients experiencing AEs in all system organ classes (SOCs), regardless of the number of SOCs in which the patient had reported events. AEs were summarised by raw incidence. Adverse Event rates per 100 patient-years of TCZ exposure (defined as the number of events divided by the sum of the total duration for each patient in the study multiplied by 100) were calculated together with the corresponding 95% CI, where applicable.

Adverse events of special interest (AESIs) were defined using published Standard MedDRA Queries (SMQs) or Adverse Event Grouped Terms (AEGTs) defined by Roche Drug Safety. The groupings of AEs included the following:

- Infections (Infections and Infestations SOC).
- Opportunistic infections (OI; Roche Standard AEGT Basket).
- Malignancies (Malignant or Unspecified tumours SMQ Narrow).
- Malignancies without NMSC.
- Hepatic events (Hepatic Failure, Fibrosis and Cirrhosis and Other Liver Damage-Related Conditions SMQ Wide or Hepatitis, non-infectious SMQ Wide).
- Stroke (Ischemic Cerebrovascular Conditions SMQ Narrow or Haemorrhagic Cerebrovascular SMQ Narrow).
- Myocardial infarction (MI; MI SMQ Narrow).
- Anaphylactic reaction events (as defined by the Roche Standard AEGT Basket according to Sampson's criteria (Sampson et al. 2006)) occurring immediately after or within 24 hours of injection of TCZ.
- Anaphylactic reaction events (as defined by the Anaphylactic Reaction SMQ Narrow) occurring immediately after or within 24 hours of injection of TCZ.
- Hypersensitivity adverse events (adverse events occurring immediately after or within 24 hours of the end of an injection that were not deemed to be 'unrelated' to study treatment).
- Gastrointestinal perforations (Gastrointestinal perforation SMQ Wide).
- Gastrointestinal perforations (Gastrointestinal perforation SMQ Wide) confirmed by medical review.
- Bleeding events (Haemorrhage terms (excluding laboratory terms) SMQ Wide).
- Demyelinating events (Demyelination SMQ Narrow).

All laboratory data were converted to Système International (SI) units and summarised with actual values as well as the change from Baseline over visits up to Week 52. Marked laboratory abnormalities were also summarised and defined using the clinical operations guidelines, Handling and Reporting of Laboratory Data. Shift tables showing the worst change from Baseline (high, normal, or low) and elevations/declines in laboratory parameters to Week 52 were also provided. Abnormal laboratory values were classified according to the NCI-CTCAE grading system (Version 4.0) and were summarised in shift tables.

Summary tables for the absolute values and changes from Baseline of the pre-injection vital sign assessments were presented by visit up to Week 52. Vital sign assessments included pulse rate,

temperature and systolic and diastolic blood pressure (after patient had been supine for at least 5 minutes). Body weight was measured at Baseline and at Weeks 12, 24 and 52. Body mass index was calculated for these time-points.

Comment: It is important to note that efficacy or safety results for Part 2 OL phase of pivotal Study WA28119 were not provided in the CSR in Module 5. The results for Part 2 OL phase of Study WA 28119 discussed in subsequent sections are based on data provided in the Clinical Summary of Safety.

9.3. Other studies

9.3.1. Other efficacy studies

Study ML25676 was a Phase II, single-centre, randomised, double blind, placebo controlled trial designed to evaluate the efficacy and safety of intravenous (IV) TCZ + prednisolone treatment compared to placebo + prednisolone treatment in the induction and maintenance of disease remission in 30 patients aged ≥ 50 years with newly diagnosed or relapsing GCA (who met the 1990 American College of Rheumatology criteria for the classification of GCA).

AE terms were coded using the MedDRA dictionary (version not provided in the publication) and their corresponding preferred terms and body systems assigned. AEs were summarised by treatment group and by body system. Details of deaths and withdrawal were summarised by treatment group. Laboratory data were summarised over time by treatment group. Changes from Baseline at each visit for each laboratory parameter were summarised using descriptive statistics.

Other supportive safety data was provided by:

1. Pooled long-term safety data with IV TCZ in the rheumatoid arthritis (RA) population, referred to as LTE All-exposure RA population. The LTE All-exposure RA data (cutoff date: 2 May 2012) includes all available data for 4171 patients from 5 Phase III, Pk and open-label studies[19]. Preferred terms were assigned by Roche to the investigator terms for diseases and AEs using MedDRA, v15.0. The International Non-proprietary Name dictionary was used to assign the preferred terms for treatments. AESIs were defined by using published SMQs or AEGTs defined by Roche Drug Safety. ISRs from Part I of Study WA28119 are presented in the context of the SC TCZ data from individual Studies WA22762 and NA25220 in RA because these events are associated with SC (and not IV) administration. The MedDRA versions used for coding AEs differed across studies;[20] and consequently, preferred terms may vary across MedDRA versions.
2. Background rates of adverse events of special interest (AESIs) and glucocorticoid- induced toxicity information from an epidemiological analysis of the MarketScan health claims database (refer to *Other safety issues* below).

[19] Five pivotal Phase III studies: Studies WA17822, (n = 622), WA17823 (n = 1190), WA18063 (n = 1216) in patients with an inadequate response to one or more disease-modifying anti-rheumatic drugs [DMARD-IR] (i.e., moderate to severe active RA population with inadequate response to MTX); Study WA17824 (n = 572) in a MTX-naïve, MTX-nonresponsive population (i.e., moderate to severe active RA patients who had not received MTX within 6 months prior to the study and who had not discontinued MTX previously for efficacy or safety reasons); Study WA18062 (n = 498) in patients with inadequate response to antitumor necrosis factor (TNF-IR) therapies.
• Drug interaction pharmacokinetics Study WP18663 (n = 23) in RA of ≥ 6 months, treated with stable dose of MTX
• Open label LTE clinical studies: – WA18695 (n = 537) in patients who completed Study WA17822; – WA18696 (n = 2066) in patients who completed Study WA17824, WA18062, or WA18063; – Study WA17823 extension.
• 6-month data from the Phase IV TCZ monotherapy Study WA19924 (n = 324) in patients with adult RA and intolerance to MTX.

[20] LTE All-exposure RA data–MedDRA v15.0; SC TCZ Studies WA22762–MedDRA v14.1 and NA25220–MedDRA v16.1; and GCA Study WA28119–MedDRA v19.0.

3. Analysis of AEs reported in single case reports of patients with GCA treated with IV TCZ outside of clinical trials. A literature review of 105 single case reports of patients with GCA, treated with IV TCZ, was performed as of 30 June 2016, but the primary focus of these published reports was on efficacy results.

9.3.2. Studies with evaluable safety data: dose finding and pharmacology

Not applicable.

9.3.3. Studies evaluable for safety only

Not applicable.

9.3.4. Studies that assessed safety as the sole primary outcome

Not applicable.

9.4. Patient exposure

In pivotal Study WA28119 (GiACTA), primary safety analysis (Part 1) was from 250[21] patients treated for 52 weeks (double blind treatment period) and the long-term extension (LTE) interim data (Part 2) from 88 patients who had at least 100 weeks of follow up in total. The LTE phase of Study WA28119 is currently ongoing.

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 randomised 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 week group (44.3 patient-years) and PBO + 52 week group (46.0 patient-years).

The median exposure to blinded SC study treatment (TCZ/placebo) was 358 days in all treatment groups. Compliance to treatment was high with median dose intensity of 100% (range of means 97.9-98.7%) across the treatment groups. The majority of patients in the TCZ QW group (82%), TCZ Q2W group (84%), PBO + 26 week group (86%) and PBO + 52 week group (80%) missed no more than 1 dose of blinded SC treatment during the 52 weeks of the study. Analysis of compliance to blinded SC treatment (TCZ/placebo) by study visit showed that although dose modifications were infrequent, the most common reason for non-compliance with study medication was that less than the full amount of the pre-filled syringe was administered.

Median total prednisone treatment duration was 52 weeks (1 year) in all treatment groups (Table 16), 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, median total cumulative prednisone dose was higher in the PBO + 26 week (3296 mg) and PBO + 52 week (3817.5 mg) groups due to increased use of escape glucocorticoid therapy (and longer prednisone taper period in the PBO + 52 week group).

[21] One patient, who was randomised to the TCZ Q2W group, withdrew the same day they were randomised, and did not receive any study treatment. This patient was excluded from the Safety analysis population.

Table 16: Exposure to all prednisone study treatment (Study WA28119, safety population)

	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)	337.2 (74.2)	338.4 (78.4)	325.3 (91.4)	325.7 (80.0)
Median	364.0	364.0	363.0	363.0
Min - Max	50 - 389	56 - 366	9 - 366	18 - 365
Treatment Duration Category (D)				
n	50	51	100	49
0 - 91	3 (6.0%)	3 (5.9%)	7 (7.0%)	1 (2.0%)
92 - 183	0	1 (2.0%)	5 (5.0%)	5 (10.2%)
184 - 274	2 (4.0%)	1 (2.0%)	2 (2.0%)	3 (6.1%)
275 - 365	44 (88.0%)	45 (88.2%)	85 (85.0%)	40 (81.6%)
>365	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Treatment Duration (W)				
n	50	51	100	49
Mean (SD)	48.1 (10.5)	48.4 (11.2)	46.5 (13.0)	46.6 (11.3)
Median	52.0	52.0	52.0	52.0
Min - Max	7 - 52	8 - 52	2 - 52	3 - 52
Treatment Duration Category (W)				
n	50	51	100	49
0 - <13	1 (2.0%)	3 (5.9%)	6 (6.0%)	1 (2.0%)
13 - <26	2 (4.0%)	1 (2.0%)	6 (6.0%)	4 (8.2%)
26 - <39	2 (4.0%)	1 (2.0%)	2 (2.0%)	4 (8.2%)
39 - <52	8 (16.0%)	4 (7.8%)	29 (29.0%)	11 (22.4%)
52 - <65	37 (74.0%)	42 (82.4%)	57 (57.0%)	29 (59.2%)
Treatment Duration (Y)				
n	50	51	100	49
Mean (SD)	0.9 (0.2)	0.9 (0.2)	0.9 (0.3)	0.9 (0.2)
Median	1.0	1.0	1.0	1.0
Min - Max	0 - 1	0 - 1	0 - 1	0 - 1
Total cumulative dose (mg)				
n	50	51	100	49
Mean (SD)	3765.2 (2022.5)	4199.0 (2291.3)	2097.8 (1248.5)	2447.0 (1827.3)
Median	3296.0	3817.5	1862.0	1862.0
Min - Max	932 - 9778	823 - 10698	630 - 6603	295 - 9913
Number of doses				
n	50	51	100	49
Mean (SD)	344.8 (103.4)	338.3 (78.6)	329.3 (106.1)	344.9 (126.8)
Median	363.0	363.0	362.0	363.0
Min - Max	56 - 854	56 - 390	8 - 860	18 - 1020

Treatment duration in days is the date of the last dose of study medication minus the date of the first dose plus one day.
Treatment duration in weeks is the last known week on Prednisone plus one week.
Treatment duration in years is the treatment duration in days divided by 365.25.

In *Part 2, open-label extension*, 88 patients had at least 100 weeks of follow-up in the study. 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 randomised to the placebo groups during Part 1, a further 16 patients received open-label TCZ during Part 2 of the study As of the data cutoff 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.

In the Phase II Study ML25676, 20 patients received TCZ + prednisolone and 10 patients received placebo + prednisolone. Prednisolone was tapered to 0 mg per day at the end of the trial in 16 (80%) and 2 (20%) patients in the TCZ and placebo groups, respectively (difference 60%, 95% CI: 30, 90). The mean follow-up time to stop prednisolone was 38 weeks (95% CI: 35, 42) and 50 weeks (95% CI: 46, 54), respectively (difference of 12 weeks, 95% CI: 7, 17; $p < 0.0001$). After 12 weeks, the median cumulative prednisolone dose was 34 mg/kg interquartile range (IQR 32 to 35) in the TCZ group and 36 mg/kg (IQR 34 to 39) in the placebo group; $p = 0.0477$). After 26 weeks and at the end of the trial, the median cumulative weight-adapted prednisolone dose was significantly higher in the placebo group (at Week 26, 41 mg/kg

(IQR 39 to 46) versus 66 mg/kg (IQR 52 to 75), respectively; p = 0.0015; and at Week 52, 43 mg/kg (IQR 39 to 52) versus 110 mg/kg (IQR 88 to 150) p = 0.005).

The LTE All-exposure RA safety dataset included data from 4171 patients with moderate to severe RA, who received at least one IV dose of TCZ in the clinical trial program and who had at least one post randomisation safety assessment providing a total of 16204.8 PY exposure. Duration of patient's participation in the study (based on the last safety information received) was summarised. This exposure (also referred to as duration in study) was used to calculate rates for AEs. Exposure to study medication (sum of actually received infusions + up to 28 days per infusion) for IV TCZ treatments (All IV TCZ Exposure RA population) was calculated. Majority of patients in the LTE All-exposure RA population were female (82%) and Caucasian (75%). Patients ranged in age from 18 to 89 years; mean (SD) age was 52.1 (12.56) years and included a variety of patient populations across the spectrum of the disease. The age of GCA patients in Study WA28119 (Part 1; mean 69.0 years across all groups; range 51 to 91 years) was older than that in the LTE All-exposure RA population (mean 52.1 years; range 18 to 89 years) which is expected as GCA affects an older population. All other key demographic characteristics (sex, height, weight and race) were generally comparable between the 2 populations. The baseline levels of acute phase reactants were lower in Study WA28119 (Part 1, CRP: range of mean across groups 6.8 to 11.4 mg/L and ESR: range of mean across groups 20.8 to 28.8 mm/hr) compared with the LTE All-exposure RA population (CRP: mean 24.4 mg/L; range 0.2 to 372 mg/L and ESR mean 46.3 mm/hr; range 0-183 mm/hr); this may have been due to fact that the patients in Study WA28119 were required to be on treatment with steroids at study entry.

9.5. Adverse events

9.5.1. All adverse events (irrespective of relationship to study treatment)

9.5.1.1. *Integrated safety analyses*

Not applicable.

9.5.1.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.5.1.3. *Pivotal and/or main efficacy studies*

Study WA28119 (Part 1, 52 week placebo controlled phase) The percentage of patients who experienced at least one AE during the 52 week double blind study period was comparable between the TCZ QW (98/100 patients (98%)), TCZ Q2W (47/49 patients (96%)), PBO + 26 week (48/50 patients (96%)) and PBO + 52 week (47/51 patients (92%)) treatment groups. The numbers of individual events was numerically or proportionally (for comparison to TCZ QW) lower in the TCZ treatment groups (470 and 486 in the placebo groups versus 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 translated into numerically higher rates of AEs in the placebo groups compared with the TCZ groups: 872 (95% CI: 813.0, 934.2), 948 (95% CI: 860.7, 1041.7), 990.8 (95% CI: 903.2, 1084.5) and 1011.2 (95% CI: 923.3, 1105.3) AEs per 100 PYs in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively. The SOC with the highest incidence of all-grade AE reporting was Infections and Infestations (75%, 74%, 76% and 65% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively)). The next highest incidence was in the Musculoskeletal and Connective Tissue Disorders SOC (63%, 57%, 68% and 63%, respectively). By preferred term, the most commonly reported all-grade AEs were non-GCA related headache (27%, 20%, 32% and 24% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively), nasopharyngitis (29%, 25%, 18% and 26%, respectively), oedema peripheral (16%, 25%, 16% and 12%, respectively) and arthralgia (13%, 16%, 22% and 16%, respectively).

No Grade 5 AEs (fatalities) were reported during Part 1 of the study. Grade 1 AEs were reported in 33%, 33%, 32% and 39% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively, Grade 2 AEs in 39%, 39%, 40% and 26%, respectively; Grade 3 AEs were reported in 24% , 22%, 22% and 26%, respectively. The SOCs with the most frequently reported Grade 3 AEs were Infections and Infestations (9%, 6%, 6% and 12%, respectively) and Musculoskeletal and Connective Tissue Disorders (5%, 6%, 4% and 4%, respectively). By preferred term, Grade 3 AEs reported by 2 or more patients in any treatment group included hypertension (3 patients in the TCZ QW group and 1 patient in each of the TCZ Q2W group, PBO + 26 week and PBO + 52 week groups), hypertensive crisis (2 patients in the TCZ QW group), leukopaenia (2 patients in the TCZ QW group), rhinitis (2 patients in the TCZ Q2W group), herpes zoster (1 patient in the TCZ QW group and 2 patients in the PBO + 52 week group), diarrhoea (2 patients in the TCZ QW group) and cataract (2 patients in the PBO + 52 week group). Grade 4 AEs were reported by only 1 patient in each treatment group (serious pulmonary embolism[22], thrombotic stroke[23], arthralgia[24] and chronic cardiac failure[25]).

Study WA28119 Part 2 (LTE): Overall, 81 of the 88 patients (92.0%) reported at least one AE in Part 2 of Study WA28119. 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; 28 severe (Grade 3) events were reported; the majority of which were from the SOCs of Infections and Infestations and Vascular Disorders. A single life-threatening (Grade 4) event and a fatal (Grade 5) event were also reported in Part 2: One patient in the PBO + 26 week group (Part 1) reported a life-threatening (Grade 4) SAE of urosepsis in Part 2. A second patient in the PBO+ 26 week group (Part 1) reported a fatal event (Grade 5) of aortic dissection in Part 2. Both of these patients were on open-label TCZ treatment at the time of these events in Part 2 of Study WA28119.

9.5.1.4. *Other studies*

ML24676: 26 AEs were reported in 15 patients (75%) in the TCZ group compared with 23 events in 7 patients (70%) in the placebo group. With the exception of infection events (10 in the TCZ group versus 1 in the placebo group) and gastrointestinal events (4 in the TCZ group versus 1 in the placebo group), the incidence of AEs was either comparable or lower in the TCZ group compared with the placebo group. No infusion-related AEs were reported. The nature of

[22] A [information redacted] male in the TCZ QW group experienced Grade 4 pulmonary embolism (serious) on Study Day 142 and was hospitalised. The event was considered unrelated to blinded study treatment (TCZ or prednisone) by the investigator but related to concurrent illness. There was no change to study treatment as a result of the event. The patient received corrective treatment with acenocoumarol and the AE was considered resolved after 11 days.
[23] An [information redacted] male in the TCZ Q2W group experienced Grade 4 thrombotic stroke (serious) on Study Day 254. The patient had been withdrawn from blinded TCZ study treatment (and blinded prednisone was interrupted) 13 days earlier due to the events of Grade 3 cellulitis and Grade 3 dry gangrene, both considered unrelated to treatment. The thrombotic stroke was considered unrelated to blinded study treatment by the investigator and all events resolved following corrective treatment.
[24] A patient in the PBO + 26 week group experienced Grade 4 arthralgia (serious) on Study Day 50 and was hospitalised. The event was considered related to blinded prednisone by the investigator. There was no change to study treatment and the AE resolved after 18 days following corrective treatment (nefopam, morphine).
[25] A [information redacted] male in the PBO + 52 week group experienced the Grade 4 AEs of chronic cardiac failure (Study Day 53, serious, unresolved), hepatic enzyme increased (Study Day 59, serious, resolved), both events which were considered related to blinded TCZ treatment by the investigator. In addition the patient experienced hypokalaemia (Study Day 97, serious, resolved), renal impairment (Study Day 97, serious, resolved) and (worsening) cardiac failure (Study Day 135, serious, unresolved), all of which were considered unrelated to blinded study treatment by the investigator.

AEs reported in the publication of this supportive study with IV TCZ was generally consistent with those reported in Study WA28119 with SC TCZ (Table 17).

Table 17: Summary of AEs: Phase II investigator-initiated Trial ML25676 (IV tocilizumab)

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.

Clinical Trial Information from Patients with RA Treated with IV Tocilizumab: The overall rates of AEs were higher in the 2 TCZ groups of Study WA28119 (Part 1) (TCZ QW = 872.0 (95% CI: 813.0, 934.2) events per 100 PY and TCZ Q2W = 948.0 (95% CI: 860.7, 1041.7) events per 100 PY) compared with the LTE All-exposure RA population (296.0 (95% CI: 293.4, 298.7) events per 100 PY). The differences in AE rates may be attributed to the much longer exposure (16204.8 PY) and follow-up (up to 5 years) in the RA population compared to the GCA population in Study WA28119 (TCZ QW = 92.9 PY and TCZ Q2W = 45.6 PY). However this data should be interpreted with caution due to major differences in the number of patients that were evaluated along with differences in background disease characteristics, patient demographics and glucocorticoid toxicity in the placebo groups in GCA (Study WA28119; Part 1). The rates of AEs were highest in the initial 6 months in Study WA28119 (Part 1) and the LTE All-exposure RA population**.** Overall, the safety profile observed with SC TCZ in GCA in Study WA28119 (Part 1; Table 18**)** was generally consistent with the established safety profile of IV TCZ in RA (Table 19), with the highest rates reported in the Infections and Infestations SOC in both populations.

Table 18: Summary of the most frequent AEs by system organ class per 100 patient years in the tocilizumab treatment groups in Study WA28119 (Part 1)

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	75 (186) 200.2 172.5, 231.2	36 (73) 160.2 125.6, 201.4
Musculoskeletal and Connective Tissue Disorders	63 (125) 134.6 112.0, 160.3	28 (73) 160.2 125.6, 201.4

PY = patient years; QW = weekly; Q2W = every other week; TCZ = tocilizumab.

Table 19: Summary of the most frequent AEs by system organ class per 100 patient years in the long term extension rheumatoid arthritis dataset

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	3183 (15026) 92.7 91.3, 94.2
Gastrointestinal Disorders	2130 (5719) 35.3 34.4, 36.2

IV = intravenous; LTE = long-term extension; PY = patient years; TCZ = tocilizumab.

9.5.2. Treatment related adverse events (adverse drug reactions)

9.5.2.1. *Integrated safety analyses*

Not applicable.

9.5.2.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.5.2.3. *Pivotal and/or main efficacy studies*

Study WA28119 (Part 1, 52 week placebo controlled phase): AEs considered related to blinded study treatment (TCZ, prednisone or both) by the investigator (that is, TCZ, prednisone or both) were reported in 68%, 74%, 64% and 53% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively. The SOCs with the highest incidence of AEs considered related to study treatment by the investigator were Infections and Infestations (most commonly (that is, ≥ 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 (LTE): Causality was not assessed for the non-serious AEs.

9.5.2.4. *Other studies*

Study ML24676: Treatment related AEs were not specified in the publication (Villiger, 2016).

9.5.3. Deaths and other serious adverse events

9.5.3.1. *Integrated safety analyses*

Not applicable.

9.5.3.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.5.3.3. *Pivotal and/or main efficacy studies*

Study WA28119 (Part 1, 52 week placebo controlled phase): No deaths were reported. The percentage of patients who experienced at least one SAE during the study was lower in the TCZ groups compared with the placebo groups (15%, 14%, 22% and 26% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively). The SAE rate per 100 PY of exposure was also numerically lower in both TCZ arms (29.1 (95% CI: 19.2, 42.3) events per 100 PY and 21.9 (95% CI: 10.5, 40.4) events per 100 PY in the TCZ QW and TCZ Q2W groups, respectively) compared with the placebo arms, with the highest AE rate per 100 PY occurring in the PBO + 52 week group (43.7 (95% CI: 27.0, 66.8) events per 100 PY) (Table 20).

Table 20: Rate of SAEs per 100 patient years (safety population)

	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 Patient Years	47.44	48.06	92.89	45.57
Number of SAEs	15	21	27	10
SAEs per patient Year	0.316	0.437	0.291	0.219
SAEs per 100 PY	31.6	43.7	29.1	21.9
95% CI	[17.7, 52.2]	[27.0, 66.8]	[19.2, 42.3]	[10.5, 40.4]

The most frequently reported SAEs occurred in the SOC of Infections and Infestations (7%, 4%, 4% and 12% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups respectively). 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 week group (and 1 patient in the TCZ QW group) and hypertensive crisis reported by 2 patients in the TCZ QW group. SAEs related to blinded study treatment (TCZ, prednisone or both) were reported in 6% (6/100) of patients in the TCZ QW group, 4% (2/49) of patients in the TCZ Q2W group, 14% (7/50) of patients in the PBO + 26 week group and 12% (6/51) of patients in the PBO + 52 week group. By preferred term, the only related SAE reported in more than 1 patient in any treatment group was herpes zoster, reported in 2 patients in the PBO + 52 week group (and 1 patient in the TCZ QW group). Other related SAEs experienced by patients in the TCZ QW group were pneumonia, gastroenteritis, pneumonia haemophilus, pyelonephritis and tachyarrhythmia and in the TCZ Q2W group were cholangitis infective and hypersensitivity. In the PBO + 26 week group other related SAEs were pneumonia, erysipelas, nasal inflammation, oropharyngeal pain, paraesthesia, syncope, glaucoma, stomatitis and arthralgia and in the PBO + 52 week group were genital herpes zoster, respiratory tract infection, dyspnoea exertional, cardiac failure chronic and hepatic enzyme increased.

Study WA28119 Part 2 (LTE): There was 1 death (fatal aortic dissection). Overall, 18 of 88 patients (20.5%) reported 23 SAEs in Part 2 of Study WA28119, majority of these SAEs represented the SOC of Vascular Disorders, with 2 events each of hematoma and temporal arteritis (GCA) and 1 event each of aortic dissection (fatal) and peripheral artery occlusion, which were likely manifestations of GCA. There were 2 events of serious infections in 2 patients (gastroenteritis and urosepsis). Of the 23 SAEs, 3 events (glaucoma, syncope and cardiac failure) were reported in patients who were never exposed to TCZ. Two events (gastroenteritis and invasive ductal breast carcinoma) were reported in patients who were in the TCZ QW group in Part 1 but were off treatment in Part 2. Two events of temporal arteritis (GCA) relapse were reported in patients treated with TCZ in Part 1 (1 patient each in TCZ QW and Q2W groups), both patients restarted TCZ treatment following the event in Part 2. The remaining 16 events occurred in patients who were on-TCZ treatment at the time of event. One Grade 4 SAE[26] and one Grade 5 SAE[27] were reported during Part 2 of the study.

[26] A [information redacted] old female, randomised in the PBO+ 26 week group in Part 1 of the study, with the diagnosis of relapsing GCA. This patient received treatment with escape prednisone in Part 1 of the study, and was considered as a non-responder. This patient received the first dose of TCZ on Study Day 365 and reported a life-threatening (Grade 4) SAE of urosepsis on Study Day 802. Study drug treatment with open-label TCZ was interrupted. This event was not considered to be related to open-label TCZ by the investigator, and the outcome was reported as not recovered/not resolved.

[27] A [information redacted] old female with a history of relapsing GCA and hypertension, randomised to the PBO+ 26 week group (Part 1). This patient had a fatal event (Grade 5) of aortic dissection in Part 2 while on treatment with open label TCZ. This event was not considered to be related to open-label TCZ by the investigator.

9.5.3.4. *Other studies*

ML24676: One cardiovascular-related death was reported in the placebo group. This patient underwent percutaneous coronary intervention for coronary artery disease and finally suffered a fatal myocardial infarction. The incidence of SAEs with IV TCZ was lower in the TCZ group (35%) compared with the placebo group (50%). No SAEs were fatal in the TCZ group.

Seven SAEs were reported in 7 patients (35%) in the TCZ group compared with 10 events in 5 patients (50%) in the placebo group. 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; 3 serious gastrointestinal complications[28] were reported in the TCZ group. 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.

Three cardiovascular SAEs were reported in the placebo group: one patient experienced syncope and a second patient underwent percutaneous coronary intervention for coronary artery disease and subsequently suffered a fatal myocardial infarction. One patient in the placebo group with previously undiagnosed diverticulosis had a sigmoid perforation. The causality of SAEs reported above in the TCZ and placebo treatment groups was not provided in the publication of this study.

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 (16 patients). The most common causes of death by preferred term included bronchopneumonia (5 patients), myocardial infarction (5 patients), pneumonia (4 patients), pulmonary embolism (4 patients), haemorrhagic stroke (3 patients), cardio-respiratory arrest (3 patients), sepsis (3 patients) and septic shock (3 patients).

The overall rates of SAEs were higher in the 2 TCZ groups of Study WA28119 (Part 1) (TCZ QW = 29.1 (95% CI: 19.2, 42.3) events per 100 PY and TCZ Q2W = 21.9 (95% CI: 10.5, 40.4) events per 100 PY) compared with the LTE All-exposure RA population (14.43 (95% CI: 13.85, 15.02) events per 100 PY). The rates of SAEs were highest in the initial 6 months in Study WA28119 (Part 1) and the LTE All-exposure RA population. Overall, the SAEs reported with SC TCZ in GCA in Study WA28119 (Part 1; Table 21) were generally consistent with the established safety profile of IV TCZ in RA (Table 22)**,** with the highest rates of SAEs reported in the Infections and Infestations SOC in both populations. In the RA LTE population, the most common individual SAEs by preferred term were pneumonia (111/4171 patients) and cellulitis (84/1471 patients). In Study WA28119 (Part 1), the most common individual SAEs by preferred terms were gastroenteritis and herpes zoster, both reported by 2 patients in the PBO + 52 week group (and 1 patient in the TCZ QW group) and hypertensive crisis reported by 2 patients in the TCZ QW group. Differences in the nature and frequency of SAEs may be attributed to the differences in the sample size between Study WA28119 (TCZ groups) and the LTE All-exposure RA population, a short duration (52 weeks) of follow-up in Study WA28119 (Part 1), or differences in background disease characteristics and patient demographics.

[28]One patient not taking prescribed pantoprazole developed a prepyloric 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.

Table 21: Summary of common SAEs by system organ class per 100 patient years in the tocilizumab 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.

Table 22: Summary of common SAEs by system organ class per 100 patient years in the long-term extension rheumatoid arthritis 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.

9.5.4. Discontinuations due to adverse events

9.5.4.1. *Integrated safety analyses*

Not applicable.

9.5.4.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.5.4.3. *Pivotal and/or main efficacy studies*

Study WA28119 (Part 1, 52 week placebo controlled phase): AEs leading to withdrawal from blinded TCZ/placebo treatment were reported in 11 patients (11%) in the TCZ QW group, 5 patients (10%) in the TCZ Q2W group, 3 patients (6%) in the PBO + 26 week group and no patient in the PBO + 52 week group. No individual AE preferred term was reported by more than 1 patient in any treatment group. Six patients in the TCZ QW group, 2 patients in the TCZ Q2W group and 1 patient in the PBO + 26 week group experienced at least one AE leading to withdrawal of study treatment, which was considered related to blinded TCZ/placebo treatment by the investigator.

Study WA28119 Part 2 (LTE): One patient died because of the SAE of aortic dissection. No other AEs led to withdrawal of patients from study treatment in Part 2 of Study WA28119.

9.5.4.4. *Other studies*

ML24676: 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). One patient died in the placebo group between Week 12 and Week 52 because of myocardial infarction. Details of AEs leading to withdrawal from study treatment were not provided in the publication of the study.

The overall rates of AEs leading to blinded TCZ withdrawal were higher in the TCZ groups in Study WA28119 (Part 1) compared with the LTE All-exposure RA population (Table 23). The differences in AE rates leading to withdrawal may be attributed to the much longer exposure and follow-up in the RA population compared with GCA, or differences in background disease characteristics and patient demographics. 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 (primarily preferred terms of pneumonia and cellulitis) and Investigations (primarily elevated transaminases) SOCs. In Study WA28119 (Part 1), no individual AE preferred term was reported by more than 1 patient in any treatment group.

Table 23: Rates of AEs leading to tocilizumab withdrawal in the tocilizumab treatment groups in Study WA28119 (Part 1) and long-term extension rheumatoid arthritis 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.

9.6. Evaluation of issues with possible regulatory impact

9.6.1. Liver function and liver toxicity

9.6.1.1. *Integrated safety analyses*

Not applicable.

9.6.1.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.6.1.3. *Pivotal and/or main efficacy studies*

Pivotal Study WA28119 (Part 1: 52 Weeks Double-Blind Treatment): The liver profile consisted of AST, ALT, total bilirubin and alkaline phosphatase. Overall, increased transaminases and elevated bilirubin were observed in a higher percentage of patients in the TCZ QW and TCZ Q2W groups than in either of the placebo groups. There were no patients who met the laboratory criteria for Hy's law, that is, no patients in this study were identified as having a > 3 x the ULN elevation in AST or ALT and 2x ULN in total bilirubin.

Mean and median ALT and AST levels in the TCZ QW group showed small increases following initiation of treatment but generally remained within the normal range. In the TCZ Q2W group mean and median ALT levels fluctuated around the baseline level throughout the study while AST levels showed a small increase which was maintained throughout the study. Mean and median ALT levels in both placebo arms showed marked decreases from Baseline which were maintained throughout the study while mean and median AST levels showed small increases from Baseline. The largest mean increase in ALT levels between baseline and Week 52 was 11.8 U/L (at Week 24) in the TCZ QW group and the largest mean change from Baseline was -8.5 U/L (at Week 24) in the TCZ Q2W group. This compares with a largest mean change from Baseline of -10.6 U/L (at Week 52) in the PBO + 26 week group and -42.6 U/L (at Week 52) in the PBO + 52 week group. For AST, the largest mean increase between baseline and Week 52 was 11.4 U/L (at Week 24) in the TCZ QW group and 7.7 U/L (at Week 32) in the TCZ Q2W group while the largest mean increases from Baseline was 2.2 U/L (at Week 16) in the PBO + 26 week group and 2.7 U/L (at Week 48) in the PBO + 52 week group. High ALT (> 110 U/L and ≥ 50% change from Baseline). Marked laboratory abnormalities were reported in 14% (14/100), 6% (3/49), 2% (1/50) and no patient in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively. High AST (> 80 U/L and ≥ 50% change from Baseline) marked laboratory abnormalities were reported in 3 patients in the TCZ QW group and 2 patients in the TCZ Q2W group. Analysis of ALT/AST levels by NCI CTC grade shows that the majority of patients across all treatment groups had normal ALT/AST levels for the duration of the study and among those with elevated ALT/AST, most experienced a Grade 1 value. One patient in each of the TCZ QW and TCZ Q2W groups had a Grade 2 elevated ALT value, while 2 patients in the TCZ QW group and 1 patient in each of the TCZ Q2W and PBO + 52 week groups experienced a Grade 3 elevated ALT value. A Grade 2 elevated AST value was reported in 1 patient in the TCZ QW group and a Grade 3 elevated AST value was reported in 1 patient in the TCZ Q2W group. 'ALT 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 week groups. 'AST 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 week 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 week group. One event of 'hepatic enzyme increased' in the PBO + 52 week group was reported as a serious AE (Grade 4) and led to TCZ study treatment interruption. None of the other events led to treatment withdrawal or study treatment interruption.

Mean and median bilirubin levels showed small increases following initiation of treatment in both TCZ treatment groups which were maintained throughout the study. There were no noteworthy changes in mean and median bilirubin levels from Baseline in the placebo groups. Markedly high bilirubin levels (> 34 µmol/L and a ≥ 75% change from Baseline) were reported in 1 patient in the TCZ QW group only. Analysis of bilirubin levels by NCI CTC grade showed that the majority of patients across all treatment groups had normal bilirubin levels over the duration of the study. Among patients developing elevated bilirubin levels, most were NCI-CTC

Grade 1 (9% (9 patients), 12% (6 patients), 2% (1 patient) and 6% (3 patients) in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively). Four patients (4%) in the TCZ QW group and 1 patient in the TCZ Q2W group was reported with Grade 2 elevated bilirubin during the study. No patients experienced Grade 3 or 4 elevated bilirubin levels.

Alkaline phosphatase levels decreased between baseline and Week 52 in both TCZ groups but showed small increases in the placebo treatment groups. Markedly high alkaline phosphatase levels (> 220 U/L and ≥ 50% change from Baseline) were not reported in any treatment group. Analysis of alkaline phosphatase levels by NCI CTC grade showed that the majority of patients across all treatment groups had normal levels over the duration of the study. Among patients developing elevated alkaline phosphatase levels, most were NCI-CTC Grade 1 (3% (3 patients), 6% (3 patients), 4% (2 patients), and 6% (3 patients) in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively). One patient in the TCZ Q2W group was reported with Grade 2 elevated alkaline phosphatase levels during the study. No patients experienced Grade 3 or 4 elevated alkaline phosphatase.

Part 2 (LTE) Laboratory data for the open label part 2 of this study was not provided.

9.6.1.4. *Other studies*

Study ML24676: No difference was observed in levels of transaminases between the TCZ and placebo groups.

9.6.2. Renal function and renal toxicity

9.6.2.1. *Integrated safety analyses*

Not applicable.

9.6.2.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.6.2.3. *Pivotal and/or main efficacy studies*

Study WA28119 Part 1: There were no clinically relevant changes in renal parameters.

9.6.2.4. *Other studies*

Study ML24676. There were no clinically relevant changes in renal parameters.

9.6.3. Other clinical chemistry

9.6.3.1. *Integrated safety analyses*

Not applicable.

9.6.3.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.6.3.3. *Pivotal and/or main efficacy studies*

Pivotal Study WA28119 (Part 1: 52 Weeks Double-Blind Treatment): The lipid profile consisted of fasting total cholesterol and LDL cholesterol. A fasting lipid profile was also to be performed in patients 8 weeks after initiation of any lipid-lowering therapy. One patient in each of the TCZ QW, TCZ Q2W and PBO + 26 week treatment groups and 2 patients in the PBO + 52 week group began taking lipid-lowering agents during the double blind period. Among patients with lipid data, the magnitude of the changes in the lipid profile observed in the TCZ arms was similar to the changes observed in the placebo arms. Mean and median fasting total cholesterol levels increased from Baseline after initiation of treatment. Levels increased by the first scheduled assessment at Week 1 and remained relatively stable thereafter. High total cholesterol (> 18.30 mmol/L and ≥ 30% increase) marked laboratory abnormalities were reported in 2 patients in each of the TCZ QW and TCZ Q2W groups, 1 patient in the PBO + 26 week group and

2 patients in the PBO + 52 week group. One patient in each of the TCZ QW, TCZ Q2W and PBO + 52 week groups had a single, not last marked abnormality and 1 patient in each treatment group had a last, or replicated marked abnormality. Analysis of cholesterol levels by NCI CTC grade showed that of those patients with a baseline and post-baseline assessment, the majority had normal levels over the duration of the study. Among patients with elevated cholesterol levels during the study, 3 patients in the TCZ QW group and 1 patient in the PBO + 26 week group developed Grade 2 elevated cholesterol. Analysis of total cholesterol levels according to the ATP III thresholds showed that, excluding patients with missing values, 18/79 patients (23%) in the TCZ QW group, 10/45 patients (22%) in the Q2W group, 8/42 patients (19%) in the PBO + 26 week group and 11/42 patients (26%) in the PBO + 52 week group had a total cholesterol level < 200 mg/dL at Baseline. After initiation of treatment, the percentage of patients who had a shift from Baseline to a worse post-baseline cholesterol value (that is, a shift to a higher ATP III category) was higher in the TCZ QW (38%; 30/79) and TCZ Q2W (40%; 18/45) treatment groups than in the PBO + 26 week (19%; 8/42) and PBO + 52 week (26%; 11/42) groups.

In both the TCZ and placebo treatment groups, mean and median fasting LDL cholesterol levels increased from Baseline after initiation of treatment. The mean increase from Baseline between Week 1 and Week 52 in the TCZ arms was similar to the mean increase observed in the placebo arms. Marked laboratory abnormalities of high LDL cholesterol (> 5.4 mmol/L and ≥ 30% increase) were reported in 2 patients in the TCZ QW and 1 patient in each of the TCZ Q2W and PBO + 26 week groups. One patient in the TCZ QW group had a single, not last marked abnormality and 1 patient in each of the TCZ QW, TCZ Q2W and PBO + 26 week groups had a last, or replicated marked abnormality. Analysis of LDL cholesterol levels by NCI CTC grade showed that 31% (31/100), 31% (15/49), 46% (23/50) and 37% (19/51) of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively had an NCI CTC Grade 2 or Grade 3 elevated LDL cholesterol level at Baseline. During the study, the percentage of patients who developed an NCI CTC Grade 2 high LDL cholesterol level, having had a Grade 0 or 1 LDL at Baseline, was 23% (23/100patients), 27% (13/49 patients), 12% (6/50patients) and 20% (10/51 patients), respectively. The percentage of patients who developed a Grade 3 high LDL cholesterol level, that did not have a Grade 3 or missing LDL at Baseline was 47% (47/100 patients), 31% (15/49 patients), 24% (12/50 patients) and 16% (8/51), respectively. Analysis of LDL cholesterol levels according to the ATP III thresholds showed that, excluding patients with missing values, 34/100 patients (34%),17/48 patients (35%), 14/50 patients (28%) and 20/48 patients (42%), respectively had a LDL cholesterol level < 100 mg/dL at Baseline. After initiation of treatment, the percentage of patients who had a shift from Baseline to a worse LDL cholesterol value (that is, a post-baseline shift to a higher ATP III category) was higher in the TCZ QW and TCZ Q2W groups (77% (77/100), 67%; 32/48), (42%; 21/50) and (48%; 23/48) in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively.

9.6.3.4. *Other studies*

Study ML24676: Total cholesterol > 5.2 mmol/L were observed in 18% and 5% of patients in the TCZ and placebo groups, respectively.

9.6.4. Haematology and haematological toxicity

There were no cases of agranulocytosis, aplastic anaemia or severe thrombocytopaenia in the clinical studies.

9.6.4.1. *Integrated safety analyses*

Not applicable.

9.6.4.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.6.4.3. *Pivotal and/or main efficacy studies*

Pivotal Study WA28119 (Part 1: 52 Weeks Double-Blind Treatment): Slight increases in mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV) and haemoglobin were observed in the TCZ arms. There were no notable changes over time for other hematologic parameters (haematocrit, RBC, monocytes, basophils and eosinophils). Marked laboratory abnormalities (that is, those outside the predefined ranges) most commonly seen were low neutrophil counts, high neutrophil counts and low WBC count. For other hematologic parameters, marked laboratory abnormalities were rare and the incidence was generally comparable between the TCZ and placebo group. Mean and median neutrophil counts decreased within the normal range after the first TCZ dose and remained at the lower end of the normal range (1.80 to 7.70 x 10^9/L) for the remainder of the 52 week treatment period. The largest mean decrease in neutrophil counts from Baseline to Week 52 was -5.2 x 10^9/L (at Week 48) in the TCZ QW group and -4.6 x 10^9/L (at Week 48) in the TCZ Q2W group. This compares with a largest mean change of -2.7 x 10^9/L (at Week 52) in the PBO + 26 week group and -2.5 x 10^9/L (at Week 52) in the PBO + 52 week group. Markedly low neutrophil counts (< 1.5 x 10^9/L and a ≥ 20% change from Baseline) were observed in 21%, 16%, 2% and 2% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively. Markedly high neutrophil counts (> 9.25 x 10^9/L and a ≥ 20% change from Baseline) were reported in 6%, 10%, 36% and 28%, respectively. Analysis of low neutrophil counts by NCI CTC grade showed that the majority of patients across all treatment groups had normal neutrophil counts for the duration of the study.

Among patients with a low neutrophil count, most experienced a Grade 1 low neutrophil count. The percentage of patients who experienced an NCI CTC Grade 2 low neutrophil count was highest in the TCZ QW group (17%, 12%, 2% and 2% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively); the percentage of patients experiencing a Grade 3 neutrophil count was 4% (4 patients) in the TCZ QW group and 4% (2 patients) in the TCZ Q2W group. One patient was reported with a Grade 3 low neutrophil count at Week 32 and experienced non-serious bronchitis and gastroenteritis (both Grade 2) at the same time. Blinded study treatment was interrupted and both events resolved. There was no association between Grade 3 low neutrophil counts and serious infections. No patients experienced a Grade 4 low neutrophil count. Neutropaenia (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 neutropaenia 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 neutropaenia. Review of the clinical listings showed that there was no association between Grade 3 or 4 events of neutropaenia and serious infections.

Mean and median platelet counts decreased after the first TCZ dose and remained at the lower end of the normal range (150-350 x 10^9/L) for the remainder of the 52 week treatment period. The mean largest decrease in platelet counts from Baseline to Week 52 was -86 x 10^9/L (at Week 48) in the TCZ QW group and -60 x 10^9/L (at Week 52) in the TCZ Q2W group. This compares with a largest mean change of -12 x 10^9/L (at Week 52) in the PBO + 26 week group and -22 x 10^9/L (at Week 32) in the PBO + 52 week group. Markedly low platelet counts (< 100 x 10^9/L and a ≥ 30% change from Baseline) were reported in 1 patient in the TCZ QW group only. This event was a single transient occurrence. Markedly high platelet counts (> 550 x 10^9/L and a ≥ 50% change from Baseline) were reported in 1 patient in the TCZ Q2W group and 1 patient in the PBO + 52 week group. Analysis of platelet counts by NCI CTC grade shows that the majority of patients across all treatment groups had normal platelet counts for the duration of the study. Among patients developing a low platelet count, all were NCI-CTC Grade 1 (7% (7 patients) in the TCZ QW group, 10% (5 patients) in the TCZ Q2W group and 1 patient in the PBO + 52 week group). Thrombocytopaenia (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 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 thrombocytopaenia events was associated with a bleeding event.

9.6.4.4. *Other studies*

Study ML24676: 9 episodes of neutropaenia (Grade ≥1) were reported in 4 patients in the TCZ group versus none in the placebo group. Fifteen episodes of thrombocytopaenia (Grade ≥ 1) were reported in 5 patients in the TCZ group compared with 4 events in 2 patients in the placebo group.

9.6.5. Other laboratory tests

Not applicable.

9.6.6. Electrocardiograph findings and cardiovascular safety

9.6.6.1. *Integrated safety analyses*

Not applicable.

9.6.6.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.6.6.3. *Pivotal and/or main efficacy studies*

ECG results were not provided in the CSR for the pivotal Study WA28119.

9.6.6.4. *Other studies*

Not provided.

9.6.7. Vital signs and clinical examination findings

9.6.7.1. *Integrated safety analyses*

Not applicable.

9.6.7.2. *Pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.6.7.3. *Pivotal and/or main efficacy studies*

In the pivotal Study WA28119, no clinically relevant mean changes from Baseline to Week 52 were observed for any vital sign parameter (BMI, diastolic and systolic blood pressure, heart rate, temperature, weight) during the study and no clinically relevant differences between the treatment groups were observed with regards to the shift from Baseline to Week 52 in BMI.

With respect to blood pressure measurements, according to the JNC 7 categories, there were no noteworthy differences in the mean changes from Baseline or NCI-CTC grade shifts from Baseline between the treatment groups.

9.6.7.4. *Other studies*

Study ML24676: Results regarding changes in vital signs were not specified in the publication (Villiger, 2016).

9.6.8. Immunogenicity and immunological events

9.6.8.1. *Integrated safety analyses*

Not applicable.

9.6.8.2. *Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

9.6.8.3. *Pivotal and/or main efficacy studies*

In the pivotal Study WA28119, of the 250 patients in the Safety population, the majority were screened for the presence of anti-TCZ antibodies and 92.2% to 98.0% of patients from all 4 treatment groups were qualified as evaluable patients. The proportions of patients in the entire study who developed treatment-induced ADA were overall low (1.1% to 6.5%) across all treatment arms; none experienced any anaphylaxis, serious / clinically significant hypersensitivity reactions, ISRs, or withdrew due to lack of efficacy. A total of 13 out of 245 patients who provided baseline samples (5.3%) had a positive screening assay at Baseline. Of these, 6 patients (1 patient from each of PBO + 52 week and TCZ QW groups and 4 patients from the TCZ Q2W group) were also positive for the confirmation assay at Baseline Post-baseline, 92.2% to 98.0% of patients from all 4 treatment groups qualified as evaluable patients (defined as a patient with a screening assay result at Baseline, at least one post-baseline sample and who has received at least one dose of study treatment). Among the evaluable patients, the proportion of patients who developed treatment induced ADAs after exposure to TCZ up to Week 52 was overall low: 1 patient (1.1%) in the TCZ QW group and 3 patients (6.5%) in the TCZ Q2W group. All 4 patients developed ADAs with neutralising potential but no patients had ADAs of the IgE isotype.

One patient in the TCZ QW group and 3 patients in the TCZ Q2W group developed treatment-induced ADAs after TCZ treatment. Among these 4 patients, none experienced any anaphylaxis, serious/clinically significant hypersensitivity, or ISRs. The overall proportion of patients withdrawn from the study due to a lack of therapeutic response was low (2.0% - 6.1%) across all treatment groups. Among patients in the Safety Population who withdrew due to lack of therapeutic response, none developed a treatment-induced ADA or an ADA of neutralising potential. Two of these patients experienced GCA flares[29]. Of the 4 patients who developed treatment-induced ADA after TCZ exposure, none became positive after dose interruptions during the study. Therefore, no patients developed treatment-induced ADA after a missing dose during the study.

9.6.8.4. *Other studies*

Study ML24676: Results regarding immunogenicity were not specified in the publication (Villiger, 2016).

9.6.9. Serious skin reactions

There were no cases of photosensitivity, erythema multiforme, drug reaction with eosinophilia and systemic symptoms or toxic epidermal necrolysis reported in the clinical studies. For injection site reactions refer to Section Adverse events of special interest. One case of Stevens-Johnson syndrome developed in a TCZ patient 3 days after the third IV infusion in study ML24676; the causal relationship could not be determined because multiple drugs had been started within the possible timeframe.

9.7. AEs of special interest

Overall, the rates of AESIs reported in Part 1 of Study WA28119 were low and the 95% CI for event rates were wide and overlapping across treatment groups. In general, the rates of events

[29] Patient in the TCZ Q2W group moved onto escape prednisone at Week 28 due to GCA flare. The patient became ADA positive at Week 24 and all subsequent visits were negative for ADA. The patient was determined by the investigator to have experienced a GCA flare at Week 28 based on signs and symptoms of GCA and an elevated ESR attributable to GCA reported at the time of flare (ESR: 37 mm/h (normal range: < 30 mm/h) at Week 28. Patient in the TCZ Q2W group became ADA positive at Week 24 and all subsequent visits were negative for ADA. The patient was determined by the investigator to have experienced a GCA flare at Week 32 based on the symptoms of PMR and an elevated ESR attributable to GCA reported at the time of flare; ESR reported as 42 mm/h (normal range: < 30 mm/h) at Week 32.

were higher during the initial 6 months of treatment in Study WA28119 (Part 1). When comparing the AESIs in the LTE All-exposure RA population with the GCA population in Study WA28119 (Part 1), the data interpretation is limited because the number of events is low in Study WA28119 (Part 1) and the 95% CI for the event rates often widely overlap.

The nature of AESIs (for example, serious infections, malignancies, strokes, hypersensitivity) from Study WA28119 (Part 1) in the GCA population was consistent with the established safety profile of IV TCZ in the RA population and no new signals are observed. There were no reports of serious bleeding, serious myocardial infarction, serious gastrointestinal perforation, serious hepatic events, serious demyelinating events and anaphylactic reactions (based on the Anaphylactic Reactions SMQ) in Study WA28119 (Part 1). 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. The 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. The nature of AESIs in Part 2 was generally consistent with that reported in Part 1 of Study WA28119.

Infections: In Part 1 of Study WA28119, there were no marked differences in the overall incidence of patients with infections between the TCZ QW (75%), TCZ Q2W (74%), PBO + 26 week (76%) and PBO + 52 week (65%) treatment groups. 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 week group and 20% of patients in the PBO + 52 week group. Overall, the rates of infections were higher in Study WA28119 (Part 1) compared with the LTE All-exposure RA population and the rate of infections was highest in the initial 6 months of treatment (see Table 24). The rates of non-serious infections are not easily captured or validated as part of health insurance claims data in the MarketScan database; and hence are not reported.

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 week group and 12% (6/51) of patients in the PBO + 52 week group (Table 25). 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 (Table 26) but with overlapping CIs.

The serious infection events of gastroenteritis and herpes zoster were both observed in 2 patients each in the PBO + 52 week 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. Serious infections resulted in the withdrawal of study treatment for 5 patients in the TCZ QW group (pneumonia, chronic sinusitis, gastroenteritis, herpes zoster and pneumonia homophiles, 1 patient in the TCZ Q2W group (cellulitis) and 1 patient in the PBO + 26 week group (pneumonia). The rates of opportunistic infections were comparable between the TCZ and placebo groups (Table 26). Opportunistic infections were reported in 2 patients in the PBO + 52 week group[30] and 1 patient in the TCZ Q2W group[31]. None of these opportunistic infections led to withdrawal of the patient from study treatment. There were no reports of tuberculosis in Study WA28119.

[30] [information redacted] old female in the PBO + 52 week group was reported with Grade 3 genital herpes zoster (serious) on Study Day 15. The patient received treatment for the event which was considered related to blinded study treatment (TCZ and prednisone) by the investigator. Blinded TCZ study treatment was interrupted and the event resolved after 27 days; [information redacted] old female patient in the PBO + 52 week group was reported with Grade 1 cytomegalovirus infection (non-serious) on Study Day 325. The patient received treatment for the event, which was considered unrelated to study treatment by the investigator. Blinded TCZ study treatment was interrupted and the event resolved after 19 days.

[31] A [information redacted] old female in the TCZ Q2W group was reported with Grade 1 oropharyngeal candidiasis (non-serious) on Study Day 8. The patient received treatment for the event, which was considered unrelated to study

Table 24: Rates of infections per 100 patient years overall and by 6 monthly periods up to 1 year, Study WA28119 (Part 1) and long-term extension rheumatoid arthritis 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.

Table 25: Summary of serious infections (Study WA28119, safety population)

MedDRA System Organ Class MedDRA Preferred Term	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	2 (4.0%)	6 (11.8%)	7 (7.0%)	2 (4.1%)
Overall total number of events	2	6	9	2
INFECTIONS AND INFESTATIONS				
Total number of patients with at least one adverse event	2 (4.0%)	6 (11.8%)	7 (7.0%)	2 (4.1%)
Total number of events	2	6	9	2
GASTROENTERITIS	0	2 (3.9%)	1 (1.0%)	0
HERPES ZOSTER	0	2 (3.9%)	1 (1.0%)	0
CELLULITIS	0	0	1 (1.0%)	1 (2.0%)
PNEUMONIA	1 (2.0%)	0	1 (1.0%)	0
CHOLANGITIS INFECTIVE	0	0	0	1 (2.0%)
CHRONIC SINUSITIS	0	0	1 (1.0%)	0
ERYSIPELAS	1 (2.0%)	0	0	0
GENITAL HERPES ZOSTER	0	1 (2.0%)	0	0
PNEUMONIA HAEMOPHILUS	0	0	1 (1.0%)	0
PYELONEPHRITIS	0	0	1 (1.0%)	0
RESPIRATORY TRACT INFECTION	0	1 (2.0%)	0	0
URINARY TRACT INFECTION	0	0	1 (1.0%)	0
UROSEPSIS	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.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Output only contains preferred terms with a Primary System Organ Class of Infections and Infestations.

treatment by the investigator. The event was considered resolved after 15 days. On Study Day 197, the patient was reported with Grade 1 laryngitis fungal (non-serious) which resolved after 85 days. No treatment was given for this event which the investigator considered unrelated to study treatment. No changes were made to study treatment.

Table 26: Overview of Serious Infections and Opportunistic Infections per 100 patient years in Study WA28119 (Part 1), long-term extension rheumatoid arthritis and giant cell arteritis market scan 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.

n 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.

The rates of serious infections (including opportunistic infections) reported in the TCZ QW group appeared numerically higher compared with the LTE All-exposure RA population and was comparable between the TCZ Q2W group and the LTE All exposure RA population. The rates for serious opportunistic infections appeared higher in the TCZ Q2W and PBO + 52 weeks groups compared with the LTE All exposure population (Table 26). However, the rates in Study WA28119 (Part 1) were based on 19 serious events and 4 opportunistic infections and the 95% CI for the rates are wide and overlapping between the 2 populations. In the LTE All-exposure RA population, the most common serious infections by preferred term were pneumonia (0.68 events per 100 PY) and cellulitis (0.52 events per 100 PY). The rates of serious infections were considerably lower in Study WA28119 compared with the MarketScan data (Table 26). The rates of opportunistic infections were comparable between Study WA28119 and MarketScan data; however, there were very few events in the study, thereby limiting clinically meaningful comparisons.

Hypersensitivity: Hypersensitivity reactions were those events which occurred during or within 24 hours of an injection (excluding ISRs) and that were not deemed unrelated to treatment. A conservative approach was taken to identify potential hypersensitivity reactions and this analysis included all AEs, regardless of whether or not they were consistent with hypersensitivity.

The rates of potential hypersensitivity reactions were comparable between the TCZ and placebo groups in Study WA28119. Potential hypersensitivity reactions were observed in 11% (11/100) of patients in the TCZ QW group, 12% (6/49) of patients in the TCZ Q2W group, 12% (6/50) of patients in the PBO + 26 week group and 6% (3/51) of patients in the PBO + 52 week group. The most frequently reported hypersensitivity events were in the SOC of Nervous System Disorders (mainly non-GCA headache and dizziness). With the exception of headache, reported in 2 patients in each of the TCZ QW and PBO + 26 week groups (and 1 patient in the PBO + 52 week group), dizziness reported in 2 patients in the TCZ QW group (and 1 patient in each of the TCZ Q2W and PBO + 26 week groups), back pain reported in 2 patients in the TCZ QW group, hyperhidrosis reported in 2 patients in the TCZ QW group and rash reported in 2 patients in the TCZ Q2W group, all other hypersensitivity events were isolated occurrences in single patients. Three patients had apparent hypersensitivity reactions, according to the algorithm described

above, which were reported as SAEs. Of these 3 patients with apparent hypersensitivity reactions, only one case was consistent with hypersensitivity from a clinical perspective[32]. Two patients[33], both in the TCZ Q2W group had clinically significant hypersensitivity reactions (that is, hypersensitivity reactions leading to withdrawal from study treatment). No other patients in any treatment group experienced a clinically significant hypersensitivity reaction.

The rates of potential hypersensitivity reactions were higher in Study WA28119 (Part 1) compared with the LTE All-exposure RA population. However, interpretation was limited because rates were based on only 52 events and low exposure in Study WA28119 (Part 1); hence the 95% CI for the rates are wide and often overlapping between the 2 populations.

Hypersensitivity reactions were not easily captured or validated as part of health insurance claims data in the MarketScan database and hence were not reported.

Injection site reactions (ISRs): In Part 1 of Study WA28119, the rate of ISRs was numerically lower in the TCZ QW group compared with the PBO + 26 week group and numerically higher in the TCZ Q2W group compared with both of the placebo groups; but with overlapping CI. AEs (all-grades) occurring at the site of a SC injection were reported in 6 patients in the TCZ QW group, 7 patients in the TCZ Q2W group, 5 patients in the PBO + 26 week group and 1 patient in the PBO + 52 week group. The only ISRs reported in more than 1 patient in any treatment group were injection site hematoma (one patient each in the PBO + 52 week and TCZ QW groups), injection site pain (one patient each in the PBO + 26 week and TCZQ2W groups) and injection site reaction (2 patients in the TCZ Q2W group). With the exception of 2 Grade 2 ISRs (injection site pain, erythema), all other ISRs were Grade 1 in severity and no ISR was reported as a SAE or required patient withdrawal from treatment.

The rates of ISRs were numerically lower in all treatment groups in Study WA28119 (Part 1) compared with those reported in the individual SC TCZ RA studies (WA22762 and NA25220). However, the rates in Study WA28119 (Part 1) were based on 20 events and the 95% CI for the rates are wide and often overlapping between the 2 populations.

Anaphylaxis: No AEs as defined by the Anaphylactic Reaction SMQ Narrow were reported. Two anaphylactic AEs (eye pruritus, dyspnoea) were identified in a single patient in the TCZ Q2W[34] group, using Sampson's criteria.

The rates for anaphylactic reactions by Sampson's criteria for the LTE All-exposure RA population were not calculated because some of the events were not confirmed to be anaphylactic reactions upon medical review. Anaphylactic reactions were not easily captured or validated as part of health insurance claims data in the MarketScan database.

Malignancies: The rates of malignancies were numerically lower in the TCZ groups compared with the placebo groups but with overlapping CIs. Malignancies were reported in 3 patients: 1

[32] [information redacted] old female patient in the TCZ Q2W group experienced Grade 3 hypersensitivity on Study Day 141. Prior to the event, the most recent dose of blinded study treatment was on Study Day 141. Up to this date, the patient had received 11 blinded SC TCZ injections and was receiving blinded prednisone according to the tapering schedule. The event was reported as serious due to hospitalization of the patient and was considered related to blinded TCZ study treatment by the investigator. The patient was withdrawn from blinded TCZ study treatment and the event resolved after 2 days.

[33] A [information redacted] year old female patient experienced Grade 3 rash with onset on Study Day 7 (within 24 hours after receiving the second blinded SC injection). The event was considered by the investigator to be related to blinded TCZ treatment, which was discontinued. The patient received treatment for the rash (fexofenadine) and the event improved. The status of the rash was unknown at the time of the data cut-off for the 52 week analysis. A 73 year-old female patient experienced Grade 3 hypersensitivity on Study Day 141 which was reported as an SAE

[34] A [information redacted] year old male patient in the TCZ Q2W group experienced the Grade 1 eye pruritus on Study Day 9 and Grade 1 dyspnoea on Study Day 10. Neither event was considered related to study treatment by the investigator. No treatment was given for the events neither of which was reported as serious. The event of dyspnoea resolved after 1 day and the event of eye pruritus resolved after 290 days. No changes were made to blinded study treatment. These events constituting an anaphylactic reaction based on Sampson's criteria were not considered to be clinically significant upon medical review. No other events of anaphylactic reactions were reported for this patient.

patient in each of the TCZ QW (marginal zone lymphoma), PBO + 26 week (breast cancer, renal neoplasm) and PBO + 52 week (malignant melanoma) groups. Of these events, breast cancer and malignant melanoma were reported as SAEs.

The rates of malignancies were numerically lower in the TCZ groups in Study WA28119 (Part 1) compared with the LTE All-exposure RA population and the MarketScan data. However, the rates in Study WA28119 (Part 1) are based on 4 events and the 95% CI for the rates are wide and overlapping between the 2 populations. In addition, the follow-up period (52 weeks) in Study WA28119 (Part 1) is considered short with respect to assessment of malignancy events.

Serious stroke events: The rates of serious stroke events were comparable between the TCZ and placebo Groups, but was based on a very small number of events (1 patient in the TCZ Q2W group[35] and 1 patient in the PBO + 52 week group. The rates of stroke events were numerically higher in the PBO + 52 week and TCZ Q2W groups in Study WA28119 (Part 1) compared with the LTE All-exposure RA population. The rates of stroke events were considerably lower in Study WA28119 (Part 1) compared with the MarketScan data. However, the rates in Study WA28119 (Part 1) are based on 2 events and the 95% CI for the rates are wide and overlapping across the populations.

Serious Bleeding, Serious Myocardial Infarction, Serious Gastrointestinal Perforation, Serious Hepatic Events, Serious Demyelinating Events: These events were not reported in Study WA28119 (Part 1), they have been reported in larger populations (that is, LTE All-exposure RA population and the MarketScan database (Table 27).

[35] an [information redacted] year-old male patient in the TCZ Q2W group experienced a Grade 4 thrombotic stroke on Study Day 254. The patient received treatment for the event which resolved after 14 days and was considered unrelated to study treatment by the investigator. The patient had previously discontinued blinded TCZ study treatment due to the separate Grade 3 AEs of cellulitis and dry gangrene.

Table 27: Overview of AEs of special interest per 100 patient-years in Study WA28119 (Part 1), long-term extension rheumatoid arthritis and giant cell arteritis MarketScan database

	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					
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.

AESIs in the open label extension of pivotal Study WA28119: A total of 8 of the 88 patients (9.1%) reported 8 AESIs in Part 2 of Study WA28119. The majority of events (3 events in 3 patients) were in the Neoplasms Benign, Malignant and Unspecified SOC (including Cysts and Polyps), with 2 events of basal cell carcinoma and 1 event of invasive ductal breast carcinoma. One of the events of basal cell carcinoma occurred in a patient who was never exposed to TCZ and the remaining 2 events of malignancy occurred in patients who were in the TCZ QW group in Part 1 and did not receive open-label TCZ in Part 2. Two events of serious infections in 2 patients (urosepsis and gastroenteritis), were reported. One event of 'troponin increased' was reported in a patient who was exposed to TCZ and 1 event of optic neuritis was reported in a patient who was in the TCZ QW group in Part 1 and did not receive open-label TCZ until after the event in Part 2. Hypersensitivity reactions during Part 2 were not evaluated. There were no AESIs reported for gastrointestinal perforation, serious/medically significant bleeding, or hepatic events.

9.8. Other safety issues

9.8.1. Safety in special populations

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

Safety based on extrinsic factors: 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 week 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. Furthermore, the duration of the study was considered too short for some of these events to manifest.

Safety in pregnancy/lactation: GCA generally occurs in the postmenopausal phase. No pregnancies occurred in the pivotal Study WA28119.

9.8.2. Safety related to drug-drug interactions and other interactions

No new data on drug interactions are available.

9.8.3. Market scan analysis of background AESI rates and glucocorticoid toxicity in GCA in absence of TCZ exposure

Background AESI rates and glucocorticoid-induced toxicity in GCA (in absence of TCZ exposure) from the MarketScan analysis were presented in Clinical summary of safety to contextualise rates reported with TCZ treatment in Study WA28119. 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. The 3 primary objectives of this study were to describe real world use of oral glucocorticoids over time in patients with GCA, estimate the incidence rates of AESIs (for example, serious hepatic events, gastrointestinal perforation, cardiovascular events and malignancies) in patients with GCA and estimate the risk of glucocorticoid-related safety events associated with cumulative glucocorticoid use over time. The Truven Healthcare MarketScan® Commercial Claims and Encounters (Commercial) database was used as the data source for the study. The commercial database contains information for patients with private-sector plans and the Medicare Supplemental and coordination of benefits. Database contains information on the Medicare population with supplemental insurance paid for by employers. Truven's Marketscan database containing about 65 million commercial and Medicare lives between 1999 and 2015 was reviewed to identify patients with GCA receiving care between 1 January 2000 and 30 June 2015. The inclusion criteria, analysis methodology and results were summarised. To increase the confidence in the accuracy of event definitions, study subjects were classified as having experienced these events if the patient had a hospitalisation (with at least one day of hospital stay) with an ICD-9 diagnosis code indicative of the following conditions that occurred on or after the index date. The only exceptions to this were malignancies and serious infections[36]. The following AESIs were identified anywhere in the available follow-up period for each patient. 1. Myocardial infarction including silent myocardial infarction 2. Ischemic stroke 3.Haemorrhagic stroke 4. Cerebrovascular accidents 5. Cardiovascular events 6. Acute coronary syndrome (hospitalisation for unstable angina) 7. Hospitalisation for heart failure 8. Acute hepatic failure 9. Hepatic transplant 10. Hepatotoxic events 11. Gastrointestinal perforation 12. Malignancies 13. Serious infections 14. Opportunistic Infections 15. Pneumonia 16. Serious Gastrointestinal bleeding events and 17. Demyelination.

The mean (SD) daily starting dose of oral glucocorticoids among all GCA patients in the MarketScan cohort (4804 patients) was 46.9 mg (34.84) and the median was 50 mg of the Real World Evidence report). The mean (SD) cumulative dose of oral glucocorticoids at 26 weeks and 52 weeks from the first glucocorticoid dose was 4171.9 mg (3,522) and 5576.9 mg (4,984), respectively. The median cumulative dose of oral glucocorticoids was 3680 mg and 4800 mg at 26 weeks and 52 weeks from the first glucocorticoid dose, respectively. One quarter of GCA patients assessed had over 5000 mg and 7000 mg of glucocorticoids by 26 and 52 weeks, respectively. Of the patients that were evaluated for their full follow-up time (median: 3 years)

[36] For malignancies, both in-patient and out-patient encounters were used and required at least 2 claims at least 7 days apart for out-patient claims on separate occasions. Serious infections were defined as any hospitalisation with an infection diagnosis or an out-patient visit in which an infection resulted in administration of intravenous antibiotics. Intravenous antibiotic therapy could not be more than 7 days before or 7 days after infection diagnosis.

in the study, the average number of days that patients were on glucocorticoids was 485 days (mean) and 338 days (median). The mean (SD) cumulative glucocorticoid dose for the full study period was 8685.9 (8,500) mg and the median was 6750 mg.

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.

Comment: It is important to note that this report uses ICD-9 billing codes from medical claims data and clinical trials including Study WA28119 (Part 1) rely on MedDRA terms from reporting physicians. Hence, the rates of AEs in this analysis are purely informative and no direct comparisons can be made.

9.8.4. Overdose, withdrawal/ rebound, safety related to driving/ operating machinery:

No new data on overdose are available. No new safety data on withdrawal and rebound are available. It is not known whether or not TCZ has an effect on the ability to drive or operate machinery. However, the pharmacologic activities and AEs reported to date do not indicate that TCZ would have such an effect.

9.9. Post marketing experience

Since TCZ is not yet approved for treatment of GCA in any country there is no post-marketing data available for GCA. However, the following information was provided in the sponsor's Clinical Summary of Safety.

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 initial market approval in Japan for the treatment of Castleman's disease on 11 April 2005 and until the end of the reporting interval of the most recent PBRER (10 April 2016), TCZ has been approved for use in over 100 countries worldwide, including the European Union and United States. Specifically, the SC TCZ formulation is approved in approximately 33 countries worldwide for the treatment of RA.

Since the International Birth Date (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). Post-marketing safety data presented in the most recent PBRER 1068646 (11 October 2015 to 10 April 2016) included non-interventional studies (NIS; including post-authorisation safety studies), reports from other solicited sources and spontaneous individual case reports (that is, reports from healthcare professionals, consumers, health authorities (worldwide) and scientific literature).

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%) (Table 28).

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 (Table 29).

Table 28: Post-marketing data: Summary tabulation of cumulative AEs by system organ class (All)

System Organ Class	No. Patients with at least 1 AE/SOC	Serious AEs		Total AEs	
		N	%	N	%
Infections and Infestations	17229	9111	21.3	25347	16.4
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	1731	1807	4.2	1985	1.3
Blood and Lymphatic System Disorders	2919	1549	3.6	3445	2.2
Immune System Disorders	1797	877	2.0	1902	1.2
Endocrine Disorders	169	89	0.2	177	0.1
Metabolism and Nutrition Disorders	1729	459	1.1	1890	1.2
Psychiatric Disorders	1452	425	1.0	1895	1.2
Nervous System Disorders	5902	2236	5.2	7880	5.1
Eye Disorders	1399	647	1.5	1842	1.2
Ear and Labyrinth Disorders	609	145	0.3	676	0.4
Cardiac Disorders	1661	1474	3.4	1951	1.3
Vascular Disorders	3310	1505	3.5	3900	2.5
Respiratory, Thoracic and Mediastinal Disorders	5457	2500	5.8	7882	5.1
Gastrointestinal Disorders	7576	3214	7.5	11617	7.5
Hepatobiliary Disorders	1446	765	1.8	1643	1.1
Skin and Subcutaneous Tissue Disorders	7366	1661	3.9	9769	6.3
Musculoskeletal and Connective Tissue Disorders	10986	3430	8.0	17999	11.7
Renal and Urinary Disorders	946	607	1.4	1097	0.7
Pregnancy, Puerperium and Perinatal Conditions	547	155	0.4	598	0.4
Reproductive System and Breast Disorders	504	229	0.5	576	0.4
Congenital, Familial and Genetic Disorders	51	41	0.1	58	0.0
General Disorders and Administration Site Conditions	16000	3872	9.0	24216	15.7
Investigations	9382	2772	6.5	15399	10.0
Injury, Poisoning and Procedural Complications	7319	2533	5.9	9727	6.3
Surgical and Medical Procedures	722	605	1.4	800	0.5
Social Circumstances	179	89	0.2	188	0.1
Total	**N/A**	**42797**	**100.0**	**154459**	**100.0**

AE = adverse event; N/A = not applicable; SOC = System Organ Class.

Table 29: Post-marketing data: summary tabulation of cumulative AEs by system organ class (subcutaneous)

System Organ Class	No. Patients with at least 1 AE/SOC	Serious AEs		Total AEs	
		N	%	N	%
Infections and Infestations	1836	553	20.8	2389	13.9
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	81	77	2.9	88	0.5
Blood and Lymphatic System Disorders	181	94	3.5	215	1.3
Immune System Disorders	177	54	2.0	181	1.1
Endocrine Disorders	12	6	0.2	13	0.1
Metabolism and Nutrition Disorders	123	23	0.9	131	0.8
Psychiatric Disorders	176	23	0.9	218	1.3
Nervous System Disorders	709	143	5.4	898	5.2
Eye Disorders	161	59	2.2	207	1.2
Ear and Labyrinth Disorders	66	12	0.5	69	0.4
Cardiac Disorders	110	82	3.1	127	0.7
Vascular Disorders	219	69	2.6	235	1.4
Respiratory, Thoracic and Mediastinal Disorders	557	166	6.2	750	4.4
Gastrointestinal Disorders	848	178	6.7	1194	7.0
Hepatobiliary Disorders	100	43	1.6	106	0.6
Skin and Subcutaneous Tissue Disorders	1069	124	4.7	1388	8.1
Musculoskeletal and Connective Tissue Disorders	1096	220	8.3	1647	9.6
Renal and Urinary Disorders	81	41	1.5	91	0.5
Pregnancy, Puerperium and Perinatal Conditions	38	6	0.2	40	0.2
Reproductive System and Breast Disorders	41	16	0.6	44	0.3
Congenital, Familial and Genetic Disorders	5	3	0.1	5	0.0
General Disorders and Administration Site Conditions	3005	331	12.4	4372	25.5
Investigations	735	149	5.6	964	5.6
Injury, Poisoning and Procedural Complications	1483	151	5.7	1706	9.9
Surgical and Medical Procedures	56	37	1.4	59	0.3
Social Circumstances	21	5	0.2	21	0.1
Total	**N/A**	**2665**	**100.0**	**17158**	**100.0**

AE = adverse event; N/A = not applicable; SOC = System Organ Class.

Off-label use in GCA: Cumulatively, as of 10 April 2016, there were 241 cases reported with an indication of GCA (preferred term: temporal arteritis). Of the 241 cases, 101 (41.9%) were reported from clinical Studies WA28119 and ML25676. The remaining 140 cases represent off-label use, of which 75 (53.6%) were reported from market research programs and patient support programs, 51 (36.4%) were spontaneous reports and 14 (10.0%) were literature reports. There is a potential for duplication of literature case reports and the individual case

reports recorded on the Company Global Safety Database[37]. Of the 140 post-marketing cases, 104 were females (74.3%), 25 (17.9%) were males and the remaining were unspecified or unknown. Of these 140 cases, 113 (80.7%) were of age ≥ 50 years, age was not reported in 26 (18.6%) and there was 1 case reported in a 29 year old. The reported cases of off-label use for GCA are consistent with the known patient demographic characteristics for this disease. The majority of these 140 post-marketing cases were reported from United States/Canada (82 (58.6%)), followed by Europe (34 (24.3%)), Switzerland (12 (8.6%)), Australia/New Zealand (6 (2.5%)), Norway (3 (2.1%)) and 1 case (0.4%) each from Brazil, Japan and Lebanon. Of these 140 post-marketing cases, there were 61 (25.3%) SAEs and there were 11 (7.9%) fatal events. SAEs were consistent with the observed safety profile of TCZ in other approved indications. Of the 11 fatal events, 4 were spontaneous reports, 4 were reported from NIS and 3 were from literature reports. All cases were medically confirmed and the 3 cases from literature reports were reported as causally related to TCZ. These 11 fatal events were categorised in the SOCs of gastrointestinal disorders, infections and infestations, cardiac disorders, general disorders and nervous system disorders.

Comment: Overall, based on the data provided no new safety concerns were identified from the post-marketing data which could potentially impact the safety profile of TCZ in the proposed GCA population.

9.10. Evaluator's overall conclusions on clinical safety

Treatment with TCZ was well-tolerated in the 52 week double blind phase (Part 1) of Study WA28119 involving 250 adult patients with GCA. Majority of patients experienced at least one AE, with the proportion of such patients ranging between 92.2% and 98.0% across treatment groups with higher rates of AEs in the placebo groups compared with the TCZ groups: PBO + 26 week group 990.8 (95% CI: 903.2, 1084.5) AEs per 100 PY; PBO + 52 week group 1011.2 (95% CI: 923.3, 1105.3) AEs per 100 PY versus 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. The incidence of SAEs (15%, 14%, 22% and 26% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively) and withdrawal due to AEs (11%, 10%, 6% and 0%, respectively) was low. No deaths were reported and no new safety signals were observed. The nature of AEs observed in the TCZ groups was similar to that in the placebo group. The most commonly reported all-grade AEs were non- GCA related headache (27%, 20%, 32% and 24% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively), nasopharyngitis (29%, 25%, 18% and 26%, respectively), oedema peripheral (16%, 25%, 16% and 12%, respectively) and arthralgia (13%, 16%, 22% and 16%, respectively). Safety of QW versus Q2W was not significantly different except for a slightly higher incidence of neutropaenia and infection with QW dosing. However, there are appropriate recommendations in proposed PI to reduce the dosing to every other week in case of ANC 0.5 to $1x10^9$cells/L.

The nature of AEs reported in the open-label LTE phase (Part 2) of Study WA28119 was generally consistent with that reported in Part 1 involving data on 88 patients on OL TCZ treatment. In both parts of the study, the highest incidence of AEs was reported in the Infections and Infestations SOC. However, the OL-LTE of this study is still ongoing and should provide more long-term safety data when completed.

Neutropaenia and thrombocytopaenia counts were the most common laboratory abnormalities observed in GCA patients treated with TCZ. The percentage of patients who experienced an NCI CTC Grade 2 low neutrophil count was 17%, 12%, 2% and 2% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively; the percentage of patients experiencing a

[37] The number of literature cases captured by the Company Global Safety Database may differ from the actual number represented in the literature due to aggregate presentation of safety data and the lack of at least one of the 4 key criteria (reporter, patient, AE, and product) required for inclusion in the Company Global Safety Database.

Grade 3 neutrophil count was 4% (4 patients) in the TCZ QW group and 4% (2 patients) in the TCZ Q2W group. No patient experienced Grade 4 neutropaenia. Review of the clinical listings showed that there was no association between neutropaenia and serious infections. Thrombocytopaenia was more common in TCZ groups, but majority were Grade 1 and none were associated with a bleeding event. Increased transaminases and elevated bilirubin were observed in a higher percentage of patients in the TCZ QW and TCZ Q2W groups than in either of the placebo groups. However, there were no patients who met the laboratory criteria for Hy's law, that is, no patients in this study were identified as having a > 3 x the ULN elevation in AST or ALT and 2x ULN in total bilirubin. Marked abnormalities in Total cholesterol and LDL levels were more commonly observed in the TCZ treatment groups compared with placebo. There were no clinically relevant changes in vital signs and ECG data was not provided.

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 week group and 12% (6/51) of patients in the PBO + 52 week group. Opportunistic infections were reported in 2 patients in the PBO + 52 week group[38] and 1 patient in the TCZ Q2W group[39]. None of these opportunistic infections led to withdrawal of the patient from study treatment. There were no reports of tuberculosis in Study WA28119. The rates of potential hypersensitivity reactions and malignancies were low and comparable between the TCZ and placebo groups. No AEs as defined by the Anaphylactic Reaction SMQ Narrow were reported; 2 anaphylactic AEs (eye pruritus, dyspnoea) were identified in a single patient in the TCZ Q2W group. The rate of ISRs was numerically lower in the TCZ QW group compared with the PBO + 26 week group and numerically higher in the TCZ Q2W group compared with both of the placebo groups; but with overlapping CI**.** Serious bleeding, serious myocardial infarction, serious gastrointestinal perforation, serious hepatic events, serious demyelinating events were not reported in Study WA28119 (Part 1), although they have been reported in larger populations (that is, LTE All-exposure RA population and the MarketScan database.

Safety data on TCZ in treatment of GCA was also provided by the Phase II Study ML25676 (only literature reference was provided), the nature of AEs reported with IV TCZ 8mg/kg IV every 4 weeks (which is not proposed route of administration for treatment) was generally consistent with those reported in Study WA28119 with SC TCZ.

The overall rate of AEs in the LTE All-exposure RA population (296.0 (95% CI: 293.4, 298.7) events per 100 PY) was lower than the rates observed in any arm of Study WA28119 (Part 1). The differences in AE rates between the GCA and RA populations may be attributed to the much longer exposure (16204.8 PY) and follow-up (up to 5 years) in the RA population compared with the GCA population in Study WA28119 (TCZ QW = 92.9 PY and TCZ Q2W = 45.6 PY) and to the differences in background disease characteristics, patient demographics and glucocorticoid toxicity in the placebo groups in GCA (Study WA28119; Part 1). In general, the rates of AEs were highest in the initial 6 months in Study WA28119 (Part 1) and the LTE All-exposure RA population. Overall, the safety profile observed with SC TCZ in GCA in Study WA28119 (Part 1) was generally consistent with the established safety profile of IV TCZ in RA (except ISRs; known

[38][information redacted] year-old female in the PBO + 52 week group was reported with Grade 3 genital herpes zoster (serious) on Study Day 15. The patient received treatment for the event which was considered related to blinded study treatment (TCZ and prednisone) by the investigator. Blinded TCZ study treatment was interrupted and the event resolved after 27 days; a [information redacted] year-old female patient in the PBO + 52 week group was reported with Grade 1 cytomegalovirus infection (non-serious) on Study Day 325. The patient received treatment for the event, which was considered unrelated to study treatment by the investigator. Blinded TCZ study treatment was interrupted and the event resolved after 19 days.

[39] A [information redacted] year-old female in the TCZ Q2W group was reported with Grade 1 oropharyngeal candidiasis (non-serious) on Study Day 8. The patient received treatment for the event, which was considered unrelated to study treatment by the investigator. The event was considered resolved after 15 days. On Study Day 197, the patient was reported with Grade 1 laryngitis fungal (non-serious) which resolved after 85 days. No treatment was given for this event which the investigator considered unrelated to study treatment. No changes were made to study treatment.

to be associated with SC administration and not IV). No new signals were observed in the pivotal Study WA28119.

The sponsor also conducted a real world data study in order to further characterise the longer-term risk associated with the use of glucocorticoids in GCA which provided evidence of a significant increase in the risk for a glucocorticoid-related AE with each 1 g increase in cumulative glucocorticoid dose. Moreover, each cumulative gram was also associated with a significant increase in risk for an AESI. This may be clinically relevant especially in light of the glucocorticoid sparing elicited by TCZ in Study WA28119, but also when considered against the observation that patients in real world clinical practice are exposed to considerably higher cumulative glucocorticoid doses than those in the Study WA28119 control groups.

Overall, the safety profile of SC TCZ in patients with GCA observed in Study WA28119 is generally consistent with that reported in the investigator-initiated Trial ML25676 in GCA with IV TCZ, the individual case reports for GCA reported in literature and with the established safety profile of IV TCZ in RA.

10. First round benefit-risk assessment

10.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Pivotal study had good study design and was well conducted involving 250 patients with active GCA. Efficacy endpoints evaluated (continuous remission and discontinuation of glucocorticoids) are valid and clinically relevant for GCA. Statistically and clinically significant treatment benefit of proposed dose of TCZ 162 mg once weekly by SC administration combined with a 26 week glucocorticoid regimen in comparison to both a short 26 weeks schedule and a longer 52 weeks schedule in terms of sustained remission at 52 weeks. Robustness of primary efficacy results confirmed in a number of sensitivity analyses designed to control for various features of the composite primary and key secondary efficacy endpoints. Reduction in risk of GCA flares in both TCZ groups compared to placebo groups. A significant glucocorticoid sparing effect of TCZ was shown. A lower proportion of patients in the TCZ treatment groups remained on active prednisone to Week 52 compared with the placebo groups. Mean annualised GCA relapse rate (which accounts for multiple flares in one patient) was lowest in the TCZ QW group.	Sustained remission rates at Week 52 were 56%, 53%, 14% and 17.6% in the TCZ QW + 26 week taper, TCZ Q2W + 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups, respectively. Proportion of patients experiencing GCA flares was 23.0%, 26.5%, 68% and 49% in the TC QW + 26 week taper, TCZ Q2W+ 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups, respectively. The median cumulative dose of prednisone at Week 52 (including all taper prednisone and escape therapy) received by the PBO + 52 week (3817.5 mg) and PBO + 26 week group (3296.0 mg) was double the cumulative doses received by the TCZ QW or Q2W groups (1862.0 mg). By Week 51 glucocorticoids were being received by 18/100 (18%) of patients in the TCZ QW group and 10/49 (20%) of patients in the TCZ Q2W group compared with 28/50 (56%) of patients in the PBO + 26 week group and 27/51 (53%) of patients in the PBO + 52 week group. Relapse rates were 0.41/yr, 0.67/yr, 1.74/yr and 1.30/yr in the TC QW + 26 week taper, TCZ Q2W+ 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups,

Indication	
Benefits	**Strengths and Uncertainties**
Efficacy demonstrated in all subgroup analyses. Health Related Quality of Life, assessed by PRO measures (SF-36, patient's global assessment VAS and FACIT-Fatigue) consistently demonstrated trends towards improvement in both TCZ treatment groups. With respect to the relative efficacy of QW and Q2W SC tocilizumab regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW tocilizumab. Moreover, consistent trends favouring QW over Q2W tocilizumab were seen for several additional endpoints and subgroup analyses. There were no new safety signals related to TCZ treatment. The profiles of both AEs and AESIs were balanced across the TCZ- and placebo treated groups, in agreement with the well characterised safety profile of TCZ in other indications.	respectively. Efficacy of TCZ 162 mg SC every week (QW) or every 2 weeks (Q2W) was observed in all subgroups based on disease onset (new onset and relapsing patients), starting prednisone dose (≤ or > 30 mg/day), by previous history of remission, by GCA diagnosis by imaging or biopsy, by GCA diagnosis based on 1990 ACR criteria or by GCA signs and symptoms at diagnosis. However, details of actual sustained remission rates at Week 52 in new onset and relapsing GCA patients was not provided. Although differences between the QW and Q2W TCZ groups were minor, there is evidence to suggest that higher exposures to TCZ following once weekly dosing regimen may potentially reduce incidence of relapse. No safety concerns were identified with more frequent QW dosing compared with the Q2W dosing with exception of increased risk of neutropaenia. However, the proposed PI has adequate recommendations for reducing dose to every other week in patients who develop neutropaenia with ANC 0.5 to 1 x 10^9 cells/L. No data on long term safety beyond 52 weeks.

10.2. First round assessment of risks

Risks	Strengths and Uncertainties
Limited evidence of efficacy and safety beyond 52 weeks. Risk of relapse following discontinuation of TCZ treatment after 52 weeks in the pivotal Study WA28119. Risk of serious infections, opportunistic infections and malignancies. Risk of neutropaenia and thrombocytopaenia. Risk of injection site reactions and hypersensitivity. Development of ADA antibodies.	Results from the ongoing pivotal Study WA28119 should provide data related to long term efficacy and safety of TCZ in treatment of GCA. This has not been evaluated adequately although it appears that risk of relapse is lesser following QW dosing compared to Q2W dosing. Serious infections reported in 7%, 4%, 4% and 12% in the TC QW + 26 week taper, TCZ Q2W+ 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups, respectively. Opportunistic infections were reported in 2 patients in the PBO + 52 week group and 1 patient in the TCZ Q2W group. None of these opportunistic infections led to withdrawal of the patient from study treatment. No reports of

Risks	Strengths and Uncertainties
	tuberculosis. The percentage of patients who experienced an NCI CTC Grade 2 low neutrophil count was 17%, 12%, 2% and 2% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively; Grade 3 neutropaenia 4%, 4% and 0%, 0%, respectively. No patient experienced Grade 4 neutropaenia. No association between neutropaenia and serious infections. Majority of thrombocytopaenia AEs were grade 1; none of these events were associated with serious bleeding. Low incidence and no ISR reported as a SAE or required withdrawal from treatment. Only 1.1-6.5% of patients overall developed treatment-induced ADA. None experienced any anaphylaxis, serious / clinically significant hypersensitivity reactions, ISRs, or withdrew due to lack of efficacy.

10.3. First round assessment of benefit-risk balance

GCA is a potentially life-threatening condition associated with substantial impairment of the day-to-day functioning of patients. There are currently no approved therapies specifically for GCA. The cornerstone of treatment is high dose glucocorticoids followed by long-term steroid tapering. Patients often experience steroid-related adverse events (AEs) due to the toxic burden of long-term, high dose steroid treatment. Prompt diagnosis and rapid initiation of treatment for GCA are critical to prevent blindness and other ischemic complications (Matteson et al. 2016). Elevated tissue and serum levels of IL-6 have been reported in the pathogenesis of GCA and correlate with disease activity. Thus, inhibition of the biological activity of IL-6 or its receptor represents a promising new approach for the treatment of GCA. Tocilizumab is a recombinant humanised, anti-human monoclonal antibody of the IgG1 subclass. The molecule targets both the soluble and membrane bound forms of the IL-6 receptor (sIL-6R and mIL-6R), adhering to the IL-6 binding site of these receptors and inhibiting IL-6 signalling in a competitive manner.

The primary and key secondary efficacy endpoints were met in the well-designed and conducted, pivotal Phase III Study WA28119 (GiACTA) that investigated the safety and efficacy of tocilizumab in 250 adult patients with active GCA. Treatment with TCZ SC 162 mg given every week or every other week along with a 26 week prednisone taper regimen produced sustained remission rates of 53-56% in the TCZ treatment groups compared with 14-17% in the placebo groups. These effects were observed in patients with new onset or relapsing disease. Primary efficacy results were supported by reduction in incidence of GCA flares and reduction in cumulative glucocorticoid dose. This reduction in steroid exposure is considered to be clinically meaningful with respect to decreasing the toxicity burden of high dose steroid exposure.

With respect to the relative efficacy of QW and Q2W SC tocilizumab regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW tocilizumab. Moreover, consistent trends favouring QW over Q2W tocilizumab were seen for several additional endpoints and subgroup analyses. Although differences between the QW and Q2W TCZ groups were minor, there is evidence to suggest that higher exposures to TCZ following once weekly dosing regimen may potentially reduce incidence of relapse although this needs to be confirmed. The proposed weekly dosing with TCZ for treatment of GCA was also

supported by PK-PD results. TCZ exposure was considerably higher (approximately 5.5 fold) following administration QW compared Q2W. Although, the logistic regression did not indicate a significant relationship between exposure and probability of REMI52, the risk of GCA flare appeared to be reduced in patients with higher exposure of TCZ; in the TCZ QW, the risk of flare was reduced by 40% and 55% for patients at the 5th and 95th exposure percentile, respectively. By contrast, for the Q2W TCZ treatment arm, risk of flare was increased by 44% for patients at 5th percentile whereas, at the 95th percentile of exposure flare risk was reduced by 46%. The annualised relapse rate up to Week 52 (ARR52) and the cumulative corticosteroid dose (CCD) also showed numerical advantages with higher TCZ exposure.

No new safety signals were observed in the study. The AEs reported were comparable between the TCZ and placebo arms and were consistent with the current TCZ profile in other indications. TCZ treatment was also associated with a clinically significant reduction in the use of steroids even within a follow-up period of only 52 weeks. No safety concerns were identified with more frequent QW dosing compared with the Q2W dosing with exception of increased risk of neutropaenia. However, the proposed PI has adequate recommendations for reducing dose to every other week in patients who develop neutropaenia with ANC 0.5 to 1x10^{9} cells/L. Although there appears to be a PK-PD relationship between decreased white blood cell counts and higher TCZ exposure, on the whole the incidence of AEs, SAEs, AEs of Infections and Infestations (II AEs) and gastrointestinal AEs (GI AEs) were not correlated with TCZ exposure.

The evidence for efficacy and safety of GCA beyond 1 year was not provided in this submission. In Study WA28119, patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open-label extension phase (Part 2) of the study. GCA is usually associated with common occurrence of disease flares during glucocorticoid dose tapering or discontinuation Therefore, it is highly likely that many patients with GCA will require treatment beyond 52 weeks in routine clinical practice. The evaluators feel that the choice to continue treatment beyond 52 weeks should be guided by disease activity, physician assessments, patient choice and emerging data including but not limited to long-term, OL data from pivotal Study WA28119.

Currently, the only treatment option for GCA is limited to glucocorticoids which are associated with significant toxicity especially following long term use. Considering the clear and long-standing unmet treatment need in GCA, the valid rationale to target IL-6, the manageable TCZ safety profile and compelling evidence of efficacy in the pivotal Phase III Study WA28119, TCZ given once weekly by SC administration along with prednisone tapering provides a viable treatment option for treatment of adults with active GCA. .

Overall, the benefit-risk balance of TCZ treatment in GCA is considered favourable.

10.4. First round recommendation regarding authorisation

Approval of Actemra (Tocilizumab 162 mg SC once weekly) is recommended for treatment of giant cell arteritis (GCA) in adult patients.

The approval is subject to the following:-

- Incorporation of suggested changes to proposed Australian PI specifically inclusion of word *'active GCA'* to reflect the patient population evaluated in the pivotal study.
- Satisfactory response to Clinical questions
- Provision of data from ongoing OL-LTE phase of Study WA29119 when it is completed.

11. Clinical questions

11.1. Pharmacokinetics

None.

11.2. Pharmacodynamics

None.

11.3. Efficacy

11.3.1. Question 1

The CSR of the pivotal Study WA28119 mentions the following: 'The proportion of patients achieving sustained remission at Week 52 was numerically higher in patients with new-onset GCA disease at Baseline compared with relapsing GCA patients. The difference in the proportion of patients achieving sustained remission at Week 52 between the TCZ groups and the PBO + 52 week group was similar among new-onset GCA patients and relapsing GCA patients. However, the difference between the TCZ groups and PBO + 26 week group was greater in relapsing GCA patients than in new-onset GCA patients mainly due to fewer relapsing patients in the PBO + 26 week group achieving sustained remission at Week 52. In both new-onset and relapsing GCA patient subgroups, the difference in the proportion of patients with sustained remission was numerically higher in the TCZ QW group compared with the TCZ Q2W group and slightly more pronounced in the relapsing patient subgroup.'

The above information was provided in the CSR but details regarding actual sustained remission rates in the new onset and relapsing GCA patients to support the above statements was not provided in the CSR. Could this information be provided to enable evaluation of actual differences between TCZ QW and TCZ Q2W groups in new onset and relapsing GCA patients?

11.3.2. Question 2

The 104 week open-label period (Part 2) is still ongoing and results were not provided in the CSR for pivotal Study WA28119. The objective of Part 2 of the study was 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. The following information was provided in the Clinical overview:

> *Patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open-label extension phase (Part 2) of the study. Preliminary data from 45 patients that met the primary endpoint in Part 1 and were followed for at least an additional 48 weeks revealed that a higher proportion of patients that previously received TCZ Q2W experienced a GCA flare (73%, 8/11) in Part 2 compared to those who previously received TCZ QW during Part 1 (33%, 8/24). This is consistent with the concept that the TCZ QW regimen may be more effective at suppressing disease activity than the TCZ Q2W dose.*

Since these results were not provided in the CSR, could the sponsors provide updated results for sustained efficacy in the ongoing OL phase of the pivotal study?

11.4. Safety

No questions.

12. Second round evaluation

12.1. Clinical Questions

The initial questions by the evaluators are mentioned first followed by a summary of the sponsor's response and the evaluator's comments on this response.

12.1.1. Efficacy

12.1.1.1. *Question 1*

The CSR of the pivotal Study WA28119 mentions the following: 'The proportion of patients achieving sustained remission at Week 52 was numerically higher in patients with new-onset GCA disease at Baseline compared with relapsing GCA patients. The difference in the proportion of patients achieving sustained remission at Week 52 between the TCZ groups and the PBO + 52 week group was similar among new-onset GCA patients and relapsing GCA patients. However, the difference between the TCZ groups and PBO + 26 week group was greater in relapsing GCA patients than in new-onset GCA patients mainly due to fewer relapsing patients in the PBO + 26 week group achieving sustained remission at Week 52. In both new-onset and relapsing GCA patient subgroups, the difference in the proportion of patients with sustained remission was numerically higher in the TCZ QW group compared with the TCZ Q2W group and slightly more pronounced in the relapsing patient subgroup.'

The above information was provided in the CSR but details regarding actual sustained remission rates in the new onset and relapsing GCA patients to support the above statements was not provided in the CSR. Could this information be provided to enable evaluation of actual differences between TCZ QW and TCZ Q2W groups in new onset and relapsing GCA patients?

Sponsor's response

The source table was in the CSR. The sustained remission rates split by disease onset was also provided in the table below for ease of reference.

Table 30: Patients achieving sustained remission at Week 52 by disease onset status

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Disease Onset Status, ITT 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 QOW + 26 Week Prednisone Taper (N=49)
New Onset Patients				
n	23	23	47	26
Sustained remission	5 (21.7%)	5 (21.7%)	28 (59.6%)	15 (57.7%)
Not sustained remission	18 (78.3%)	18 (78.3%)	19 (40.4%)	11 (42.3%)
Relapsing Patients				
n	27	28	53	23
Sustained remission	2 (7.4%)	4 (14.3%)	28 (52.8%)	11 (47.8%)
Not sustained remission	25 (92.6%)	24 (85.7%)	25 (47.2%)	12 (52.2%)

Patients in remission will be classed as responders.
Patients are in sustained remission when they are responders from Week 12 to Week 52.
Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
Elevated ESR which attribute to GCA is reflected in Flare by investigator.
Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
Percentages are based on n.

Evaluator's response

The sponsor's response is satisfactory.

12.1.1.2. *Question 2*

The 104 week open-label period (Part 2) is still ongoing and results were not provided in the CSR for pivotal Study WA28119 in Module 5. The objective of Part 2 of the study was 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. The following information was provided in the Clinical overview:

> *Patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open-label extension phase (Part 2) of the study. Preliminary data from 45 patients that met the primary endpoint in Part 1 and were followed for at least an additional 48 weeks revealed that a higher proportion of patients that previously received TCZ Q2W experienced a GCA flare (73%, 8/11) in Part 2 compared to those who previously received TCZ QW during Part 1 (33%, 8/24). This is consistent with the concept that the TCZ QW regimen may be more effective at suppressing disease activity than the TCZ Q2W dose.*

Since these results were not provided in the CSR, could the sponsors provide updated results for sustained efficacy in the ongoing OL phase of the pivotal study?

Sponsor's response

The Summary of Clinical Efficacy contains the data (see also table below) from the open label period available at the time of dossier preparation. There are no plans for a formal interim analysis in the ongoing Part 2 open label phase of the study. The final Part 2 Clinical Study Report will be available in Q1 2019.

Table 31: 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%)

Evaluator's response

The sponsor's response is satisfactory.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Actemra in the proposed usage are unchanged from those identified in the first round evaluation.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Actemra in the proposed usage are unchanged from those identified in the first round evaluation.

13.3. Second round assessment of benefit-risk balance

The benefit risk balance of Actemra for treatment of GCA is favourable.

13.4. Second round recommendation regarding authorisation

Approval of Actemra (Tocilizumab 162 mg SC once weekly) is recommended for treatment of giant cell arteritis (GCA) in adult patients.

The approval is subject to the following:

- Incorporation of suggested changes to proposed Australian PI, and
- Assurance that sponsors will provide data from ongoing OL-LTE phase of Study WA29119 when it is completed (expected to complete in Q1 2019).

14. References

Adizie T, Christidis D, Dharmapaliah C, et al. Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. Int J Clin Pract. 2012;66(9):906-9

Adler S, Reichenbach S, Kuchen S, et al. Termination of Tocilizumab-Treatment in Giant Cell Arteritis: Follow-up of Patients after the RCT (ClinicalTrials.gov registration number: NCT01450137). ACR/ARHP Annual Meeting 2016, Abstract number: 867, date of first publication: September 28, 2016.

Alba MA, García-Marinez A, Prieto-González S, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine. 2014;93(5):194- 201.

Andersson R, Malmvall BE, Bengtsson BA. Long-term corticosteroid treatment in giant cell arteritis. Acta Med Scand. 1986;220:465-9.

Beyer C, Axmann R, Sahinbegovic E, et al. Anti-IL6 receptor therapy as rescue treatment for giant cell arteritis. Ann Rheum Dis 2011;70(10):1874-5.

Borchers AT and Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev. 2012;11:A544-A554.

Borchers AT and Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev. 2012;11:A544-A554.

Brack A, Martinez-Taboada V, Stanson A, et al. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum. 1999;42(2):311-7.

Broder MS, Sarsour K, Chang E, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis. Sem Arthr Rheum. 2016, in press (doi:10.1016/j.semarthrit.2016.05.009).

Butler N, Mundy J, Shah P. Aortic Complications of Giant Cell Arteritis: A Diagnostic and Management Dilemma. J Card Surg. 2010;25:572-581.

Chandran AK, Udayakumar PD, Crowson CS, et al. The Incidence of Giant Cell Arteritis in Olmsted County Minnesota, Over a Sixty Year Period 1950 - 2009. Scand J Rheumatol. 2015;44(3):215-218.

Christidis D, Jain S, Das Gupta B. Successful use of TCZ in polymyalgic onset biopsy positive gca with large vessel involvement. BMJ Case Reports 2011;doi: 10.1136/bcr.04.2011.4135.

Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR Guidelines for the management of giant cell arteritis. Rheumatol. 2010:49:1594-1597.

Dayer JM and Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. Rheumatology. 2010;49:15-24.

Gonzàlez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009;61(10):1454-61.

Hoffman GS, Cid MC, Hellmann DB, et al. A multicenter, randomised, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46(5):1309-18.

Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomised trial. Ann Intern Med. 2007;146(9):621-30.

Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33:1122-8.

Jover JA, Hernández-García C, Morado IC, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;134(2):106-14.

Kobayashi S, Yano T, Matsumoto Y, et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. Arthritis Rheum. 2003;49(4):594-8.

Langford CA, Cuthbertson D, Ytterberg SR. A Randomized Double-Blind Trial of Abatacept and Glucocorticoids for the Treatment of Giant Cell Arteritis [abstract]. Arthritis Rheumatol. 2015;67(suppl 10).

Mahr AD, Jover JA, Spiera RF, et al. Adjunctive Methotrexate for Treatment of Giant Cell Arteritis - An Individual Patient Data Meta-Analysis. Arthritis Rheum. 2007;56:2789-2797.

Matteson EL, Buttgereit F, Dejaco C, et al. Glucocorticoids for Management of Polymyalgia Rheumatica and Giant Cell Arteritis. Rheum Dis Clin N Am. 2016;42:75-90.

Mazlumzadeh M, Hunder GG, Easley KA, et al. Treatment of Giant Cell Arteritis Using Induction Therapy With High-Dose Glucocorticoids. Arthritis Rheum. 2006;54:3310-3318.

Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68:318-23.

Nesher G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: A 15-year survey of 43 patients. Rheumatol. 1994;21:1283-1286.

Nuenninghoff DM, Hunder GG, Christianson TJH, et al. Incidence and Predictors of Large-Artery Complication (Aortic Aneurysm, Aortic Dissection and/or Large- Artery Stenosis) in Patients With Giant Cell Arteritis. Arthr Rheum. 2003a;48:3522-3531.

Petri H, Nevitt A, Sarsour K, et al. Incidence of giant cell arteritis and characteristics of patients: Data-driven analysis of comorbidities. Arthritis Care and Research. 2014;1-24

Proven A, Gabriel SE, Orces C, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703-8.

Quartuccio L, Maset M, De Maglio G, et al. Role of oral cyclophosphamide in the treatment of giant cell arteritis. Rheumatology. 2012;51(9):1677-86.

Salvarani C, Magnani L, Catanoso M, et al. Tocilizumab : a novel therapy for patients with large-vessel vasculitis. Rheumatology (Oxford) 2012;51(1):151-6.

Schaufelberger C, Andersson R, Nordborg E. No additive effect of cyclosporin A compared with glucocorticoid treatment alone in giant cell arteritis: results of an open, controlled, randomized study. Br J Rheumatol. 1998;37(4):464-5.

Sciascia S, Piras D, Baldovino S, et al. Mycophenolate mofetil as steroid-sparing treatment for elderly patients with giant cell arteritis: report of three cases. Aging Clin Exp Res. 2012;24(3):273-7.

Seitz M, Reichenbach S, Bonel HM, et al. Rapid induction of remission in large vessel vasculitis by IL-6 blockade: a case series. Swiss Med Wkly 2011;141:w13156

Seror R, Baron G, Hachulla E, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicenter randomised controlled trial. Ann Rheum Dis. 2014 Dec; 73(12):2074–81, Epub 2013 July 29.

Smith CA, Fidler WJ, Pinals RS, et al. The epidemiology of giant cell arteritis. Report of a ten-year study in Shelby County, Tennessee. Arthritis Rheum. 1983;26(10):1214-9.

Spiera RF, Mitnick HJ, Kupersmith M, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol. 2001;19(5):495-501.

Unizony S, Arias-Urdaneta L, Miloslavsky E, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, takayasu arteritis) and polymyalgia rheumatica. Arthritis Care Res (Hoboken) 2012;64(11):1720-9.

Villiger PM, Adler, S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387:1921-27.

Warrington KJ and Weyand CM. Giant Cell Arteritis and Polymyalgia Rheumatica.Oxford Textbook of Vasculitis. Ed: Ball, Fessler, Bridges. Chapter 2. 2014.

Weyand C and Goronzy J. Giant-cell arteritis and polymyalgia rheumatica. N Engl J Med. 2014;371(1):50-57.

Weyand C and Goronzy J. Giant-cell arteritis and polymyalgia rheumatica. Ann Intern Med. 2003;139:505-515.

Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. J Biopharm Stat. 2009 Nov;19(6):1085–98.

Yates M, Loke YK, Watts RA, et al. Prednisolone combined with adjunctive immunosuppression is not superior to prednisolone alone in terms of efficacy and safety in giant cell arteritis: meta-analysis. Clin Rheumatol. 2014;33:227-236.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au