Official Title: A Phase Ib, Open-Label, Dose-Ranging Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Tocilizumab Administered by Intravenous Infusion to Patients With Giant Cell Arteritis

NCT Number: NCT03923738

Document Date: Protocol Version 4: 06-September-2019

PROTOCOL

TITLE:	**A PHASE Ib, OPEN-LABEL, DOSE-RANGING STUDY TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF TOCILIZUMAB ADMINISTERED BY INTRAVENOUS INFUSION TO PATIENTS WITH GIANT CELL ARTERITIS**
PROTOCOL NUMBER:	WP41152
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-004718-17
IND NUMBER:	113,654
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	12 December 2018
DATES AMENDED:	Version 2: 19 February 2019 Version 3: 11 April 2019 Version 4: See electronic date stamp below.

FINAL PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
06-Sep-2019 16:16:06	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

Protocol WP41152 has been amended to modify the exclusion criterion for absolute neutrophil count (ANC). Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 4.1.2 (Exclusion Criteria) has been revised to change the exclusion criterion for ANC from $<2.0\times10^9$/L (2000/mm^3) to $<1.5\times10^9$/L (1500/mm^3).

  Historically, tocilizumab (TCZ) protocols recruiting TCZ-naive patients have used an exclusion criterion for neutrophils of $<2.0\times10^9$/L, and this value was used in the WP41152 study. However, since Study WP41152 is recruiting patients already receiving TCZ and TCZ treatment is associated with a higher incidence of neutropenia, many patients being screened for this study are failing to meet the eligibility criteria because they have an ANC count below 2.0×10^9/L.

  ANC values in the $1.5–2.0\times10^9$/L range are not considered clinically significant in TCZ-treated patients, and per the TCZ Swiss Prescribing Information risk mitigation guidelines, it is recommended that TCZ therapy is maintained unless ANC falls below 1.0×10^9/L.

  The protocol is therefore being amended to allow patients with an ANC of $\geq1.5\times10^9$/L to participate in the study.

- In order to address the feedback from the Ethics Committee in Switzerland (where this study will be conducted), Section 4.5.7 (Laboratory, Biomarker, and Other Biological Samples) has been updated to provide details of the external laboratories used in Study WP41152, which will analyze and store samples until they are destroyed upon completion of the clinical study report.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib, OPEN-LABEL, DOSE-RANGING STUDY TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF TOCILIZUMAB ADMINISTERED BY INTRAVENOUS INFUSION TO PATIENTS WITH GIANT CELL ARTERITIS**
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PHASE:	Phase Ib
INDICATION:	Giant cell arteritis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the pharmacokinetics, pharmacodynamics, and safety of 6 and 7 mg/kg of tocilizumab (TCZ) administered by IV infusion every 4 weeks (Q4W) to patients with giant cell arteritis (GCA). Specific objectives and corresponding endpoints for the study are outlined below.

Pharmacokinetic Objectives

The primary pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of two dose levels of TCZ administered by IV infusion to patients with GCA, on the basis of the following endpoints:

- Steady-state maximum serum concentration (C_{max}) at specified timepoints
- Trough concentration (C_{trough}) at specified timepoints
- Area under the concentration–time curve (AUC) over the dosing interval of 4 weeks (AUC_{4weeks}) at specified timepoints

Pharmacodynamic Objectives

The pharmacodynamic (PD) objective for this study is to assess the pharmacodynamics of two dose levels of TCZ administered by IV infusion to patients with on the basis of the following endpoints:

- Serum concentration of interleukin-6 (IL-6) at specified timepoints
- Serum concentration of soluble interleukin-6 receptor (sIL-6R) at specified timepoints
- Serum concentration of C-reactive protein (CRP) at specified timepoints
- Erythrocyte sedimentation rate (ESR) at specified timepoints

Safety Objectives

The safety objective for this study is to evaluate the safety and tolerability of two dose levels of TCZ administered by IV infusion to patients with GCA on the basis of the following endpoints:

- Nature, frequency, severity, and causality of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0

- Clinical safety laboratory results

Exploratory Objective

The exploratory objective for this study is to monitor the efficacy of two dose levels of TCZ administered by IV infusion to patients with GCA on the basis of the following endpoints:

- Proportion of patients who experience a flare, defined as the recurrence of signs or symptoms of GCA and/or ESR $\geq$ 30 mm/h attributable to GCA as determined by the investigator, during each period
- Proportion of patients in remission, defined as the absence of flare (defined above) and normalization of CRP ($<$ 1 mg/dL), at each visit

Study Design

Description of Study

This is a Phase Ib, open-label, dose-ranging study designed to characterize the pharmacokinetics, pharmacodynamics, and safety of two dose levels of TCZ (6 and 7 mg/kg) administered by IV infusion Q4W to patients with GCA. This study will enroll patients with GCA from at least two sites in Switzerland who have received at least five consecutive doses of 8 mg/kg TCZ IV Q4W prior to baseline in clinical practice and who have reached remission, defined as the absence of flare and normalization of CRP ($<$ 1 mg/dL).

The study is divided into two periods: In Period 1, approximately 25 patients who have been receiving 8 mg/kg TCZ IV Q4W for a minimum of five consecutive doses and who are in remission will receive five consecutive doses of 7 mg/kg TCZ IV Q4W. Subsequently, if a patient is still in remission at the end of Period 1, the patient will enter Period 2 and receive five consecutive doses of 6 mg/kg TCZ IV Q4W. Although five doses at each dose level are sufficient to achieve the primary study objectives, if absolutely necessary to accommodate patient availability for the intensive PK sampling during the last dosing cycle, the dosing periods may be extended by one dose for a total of six doses. This will not be considered a protocol violation.

The plan is to enroll approximately 25 patients into Period 1 in order to obtain data to robustly characterize the pharmacokinetics at each of the two dose levels. Guidance from a statistical evaluation of the variability in PK parameters from IV dosing established a minimum of 12 patients would be adequate. Given the open-label nature of the study design, an evaluation of the data at the end of Period 1 will be undertaken. If the dropout rate and/or variability are higher than planned, additional patients on 8 mg/kg TCZ IV Q4W (who have received at least five consecutive doses and are in remission) may be directly enrolled into Period 2. Because the study design allows sufficient time to achieve steady state at the 6 mg/kg dose level, there is minimal influence from the small difference expected in PK and PD outcomes from prior dosing with 8 mg/kg versus 7 mg/kg; hence the protocol allows for direct enrollment of patients who had received either 8 mg/kg or 7 mg/kg TCZ IV Q4W into Period 2. Data from all patients receiving 6 mg/kg TCZ IV Q4W in Period 2 will be combined.

PK samples will be obtained before and after each infusion of TCZ to characterize the C_{max} and C_{trough} of TCZ, and more intensive sampling during the last dosing cycle will be used to estimate the steady-state AUC_{4weeks} at each dose level.

The usage of glucocorticoids during the study is at the discretion of the investigator. Only patients in remission at the end of Period 1 will be eligible for Period 2.

Number of Patients

The study will enroll approximately 25 adult patients with a diagnosis of GCA who are being treated with 8 mg/kg TCZ IV Q4W in clinical practice and have reached remission at the time of enrollment.

Target Population

Inclusion Criteria

Patients entering Period 1 or Period 2 directly (without prior participation in Period 1) must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 50 years at time of signing Informed Consent Form

- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of GCA classified according to the following criteria:
  - Age ≥ 50 years
  - History of ESR ≥ 50 mm/hour *

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

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

  AND at least one of the following:
    - Temporal artery biopsy revealing features of GCA
    - Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), or positron emission tomography-computed tomography (PET-CT)
- For patients entering Period 1: patients must be receiving treatment with TCZ 8 mg/kg IV Q4W and have received at least five consecutive doses prior to baseline and be in remission at baseline.
- For patients entering Period 2 after completing Period 1: prior to the first dose of 6 mg/kg TCZ IV, patients must be in remission at the end of Period 1.
- For patients entering Period 2 directly (without prior participation in Period 1): patients must be receiving treatment with TCZ 8 mg/kg IV Q4W and have received at least five consecutive doses prior to the first study visit in Period 2 and be in remission at the first study visit in Period 2.
- For women: not of childbearing potential. A woman is considered to be not of childbearing potential if she has reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause) or has undergone surgical sterilization (removal of ovaries and/or uterus). The definition of non-childbearing potential may be adapted for alignment with local guidelines or requirements.
- For men: not of reproductive potential (i.e., infertile or sterilized) or agreement to use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must use a condom during the treatment period and for at least 28 days after the final dose of TCZ. Men must refrain from donating sperm during this same period.

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

- Lack of peripheral venous access
- Major surgery within 8 weeks prior to screening, or planned major surgery during the study
- Organ transplant (except corneal transplant performed more than 3 months prior to screening)
- Major ischemic event, related or unrelated to GCA, within 12 weeks prior to screening
- Treatment with any other investigational agent besides TCZ within 12 weeks (or 5 half-lives of the investigational drug, whichever is longer) prior to screening

- Previous treatment with cell-depleting therapies, including investigational agents, including, but not limited to, Campath® (alemtuzumab), anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20
- Treatment with IV gamma globulin or plasmapheresis within 6 months prior to baseline (Day 1)
- Previous treatment with alkylating agents, such as chlorambucil, or with total lymphoid irradiation
- Immunization with a live or attenuated vaccine within 4 weeks prior to baseline
- Treatment with hydroxychloroquine, cyclosporine A, azathioprine, or mycophenolate mofetil within 4 weeks prior to baseline (Day 1)
- Treatment with other biologics (e.g., etanercept, infliximab, certolizumab, golimumab, abatacept, adalimumab, anakinra) or targeted synthetic disease-modifying anti-rheumatic drug (e.g., tofacitinib, baricitinib) within 12 weeks prior to baseline (Day 1)
- Treatment with cyclophosphamide within 6 months of baseline (Day 1)
- History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies (including history of discontinuation of TCZ due to any infusion-related reaction or hypersensitivity)
- Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), psychiatric, osteoporosis or osteomalacia, glaucoma, corneal ulcers or injuries, or gastrointestinal (GI) disease
- Current liver disease, as determined by the investigator
- History of diverticulitis, diverticulosis requiring antibiotic treatment, or chronic ulcerative lower GI disease such as Crohn disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose a patient to perforations
- Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including, but not limited to, tuberculosis [TB] and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of the nail beds)
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks of screening
- Active TB requiring treatment within the previous 3 years

  Patients should be screened for latent TB and, if positive, treated according to local practice guidelines prior to baseline.

  Patients treated for TB with no recurrence within the last 3 years and patients treated for latent TB within last 3 years are eligible.
- Primary or secondary immunodeficiency (history of or currently active)
- Evidence of malignant disease or malignancies diagnosed within the previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that have been excised and cured)
- History of alcohol, drug, or chemical abuse within 1 year prior to screening
- Body weight $>$ 150 kg

At screening:

- Serum creatinine $>$ 1.4 mg/dL (124 μmol/L) in female patients and $>$ 1.6 mg/dL (141 μmol/L) in male patients
- ALT or AST $>$ 1.5 $\times$ upper limit of normal (ULN)
- Total bilirubin $>$ ULN
- Platelet count $< 100 \times 10^9$/L (100,000/mm^3)
- Hemoglobin $<$ 85 g/L (8.5 g/dL; 5.3 mmol/L)
- WBCs $< 3.0 \times 10^9$/L (3000/mm^3)

- ANC $< 1.5 \times 10^9$/L (1500/mm^3)
- Absolute lymphocyte count $< 0.5 \times 10^9$/L (500/mm^3)
- Positive hepatitis B surface antigen test or positive hepatitis C antibody test

End of Study

The end of this study is defined as the date when the last patient, last visit occurs, which corresponds to approximately 28 days after the last dose. The end of the study is expected to be approximately 10 months after enrollment of the last patient into Period 1.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 12 months.

In addition, the Sponsor may decide to terminate the study at any time.

Investigational Medicinal Products

The investigational medicinal product for this study is TCZ.

Test Product (Investigational Drug)

TCZ will be administered by IV infusion at doses of 7 or 6 mg/kg Q4W. The maximum dose of TCZ that will be administered is 800 mg. The dose of TCZ infusion will be calculated on the basis of body weight measured prior to each infusion.

Statistical Methods

Primary Analysis

Given the small sample size, the short duration of the study, and open-label design without a control arm, a dose-related effect on flares is not expected to be observed. Sample size estimates are entirely based on PK data. PK, PD, safety, and efficacy data will be summarized descriptively. No formal statistical hypothesis testing is planned. A database lock will occur when the last patient has completed the final visit 28 days after the final dose.

The primary PK variables in this study are estimates of steady-state C_{trough}, C_{max}, and AUC_{4weeks} at the two dose levels of TCZ IV therapy (7 mg/kg Q4W and 6 mg/kg Q4W). For each dose level, C_{trough} and C_{max} will be summarized at each timepoint for each dose administered and AUC_{4weeks} estimated for the last dosing cycle will be summarized as geometric means, medians, ranges, and standard deviations.

Determination of Sample Size

In order to provide a precise characterization of PK parameters (C_{trough}, C_{max}, and AUC_{4weeks}), in this study, a hybrid of two approaches will be followed. The first of these approaches is the guidance for estimation of sample size in pediatric studies, which requires a study to be prospectively powered to target 95% CI within 60%−140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric sub-group with at least 80% power. The second is the sample size guidance from the Food and Drug Administration for bioequivalence studies, which specifies the 90% CI for the geometric mean ratio (GMR) should fall within 80%–125% of the GMR estimate.

Given the need to characterize the PK parameters to a higher precision than in a pediatric population, the sample size for this study was estimated based on achieving a target of 95% CI for estimates of C_{max} and C_{trough} at each dose level that would fall within 80%−125% of the geometric mean estimate.

In Study ML25676, observed steady-state C_{trough} data were available for 18 patients receiving 8 mg/kg TCZ IV Q4W. The geometric mean was 44.4 μg/mL (95% CI: 37.0, 53.4), with the 95% CI corresponding to 83% and 120% of the geometric mean estimate.

Using the variability in observed steady-state C_{trough} in Study ML25676, a sample size of $n = 17$ will provide $> 80\%$ power to characterize the geometric mean estimate of the observed C_{trough} and C_{max} so that the 95% CI falls within 80%−125% of the geometric mean estimate of the corresponding PK parameter. A minimal sample size of $n = 12$ would provide $> 80\%$ power for the 90% CI to fall within 80%–125% of the geometric mean estimate of the corresponding PK parameter. To account for potential study dropouts, approximately 25 patients already receiving 8 mg/kg IV TCZ and in remission will be enrolled in the Period 1 of this study with the goal of obtaining robust PK characterization at both dose levels.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AUC	area under the concentration–time curve
AUC_{4weeks}	area under the concentration–time curve over 4 weeks (the dosing interval)
$C_{average}$	average concentration
CL	clearance
C_{max}	maximum serum concentration
C_{trough}	trough concentration
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine-release syndrome
CS	corticosteroid
CSR	Clinical Study Report
CTA	computed tomography angiography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DIBD	Development International Birth Date
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
GC	glucocorticoid
GCA	giant cell arteritis
GI	gastrointestinal
GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
ICH	International Council for Harmonisation
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MRA	magnetic resonance angiography
NCEP	National Cholesterol Education Program

Abbreviation	Definition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	*pharmacodynamic*
pJIA	polyarticular juvenile idiopathic arthritis
Pop PK	population pharmacokinetics
PET-CT	positron emission tomography- computed tomography
PK	pharmacokinetic
PMR	polymyalgia rheumatica
PY	Patient years
Q2W	every 2 weeks
Q4W	every 4 weeks
QW	once a week
RA	rheumatoid arthritis
sIL-6R	soluble interleukin-6 receptor
sJIA	systemic juvenile idiopathic arthritis
TAK	Takayasu arteritis
TB	tuberculosis
TCZ	tocilizumab
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON GIANT CELL ARTERITIS

Giant cell arteritis (GCA; or temporal arteritis) is the most common primary systemic vasculitis. GCA affects large- and medium-sized arteries and occurs almost exclusively in adults older than 50 years. The incidence increases with age and peaks during the eighth decade; the mean age at diagnosis is approximately 75 years. GCA is 2 to 3 times more common in women than in men. The reported prevalence of documented GCA in populations aged over 50 years varies significantly geographically and ranges between 24 and 200–278 per 100,000 people in the European Union and United States, respectively (Salvarani et al. 2004; Lawrence et al. 2008; Lee et al. 2008). GCA can manifest with ischemic events due to vessel occlusion, most typically central retinal artery occlusion or anterior ischemic optic neuropathy, both of which lead to irreversible vision loss. In the past 25 years, awareness of the prevalence of aortitis that frequently leads to aneurysm and large-vessel vasculitis affecting the primary aortic branches has grown (Kermani et al. 2013).

Until recently, corticosteroids (CS's) were the mainstay of treatment for GCA. Typically, oral prednisone or prednisolone is used, although some physicians use pulsed IV CS's in patients presenting with visual loss. Although CS's are highly effective at inducing remission of systemic inflammation and preventing acute damage (e.g., blindness), their use comes with a high toxicity burden, with 86% of patients experiencing CS-related adverse clinical events at 10-year follow-up (Proven et al. 2003). Among the most deleterious of these effects are osteoporosis, hypertension, hyperglycemia, and increased body mass (and redistribution of body fat). In addition, CS's are not as effective at maintaining remission, with many patients (up to 50%) experiencing relapse or flare-up of symptoms during reduction or discontinuation of CS's (Proven et al. 2003).

Various agents, including azathioprine, cyclophosphamide, methotrexate, infliximab, and etanercept, have shown conflicting or no evidence of benefit in the treatment of GCA. In spite of the paucity of evidence, methotrexate is used inconsistently as standard-of-care treatment for CS sparing in patients with refractory disease. Supportive therapies that have a place in standard-of-care treatment include antiplatelet agents (typically 5-aminosalicylic acid or aspirin) and preventative therapies for osteoporosis according to local practice.

In 2017, the SC formulation of the anti–interleukin-6 receptor (IL-6R) antibody tocilizumab (TCZ) was approved for the treatment of GCA in the United States, European Union, Switzerland, and other countries based on the results from the Phase III WA28119 (GiACTA) study (see Section 1.2 for background on TCZ and Section 1.2.1.2 for additional information on Study WA28119).

1.2 BACKGROUND ON TOCILIZUMAB

TCZ is a recombinant humanized, anti-human monoclonal antibody of the IgG1 subclass directed against soluble and membrane-bound IL-6R. TCZ binds specifically to both soluble IL-6R (sIL-6R) and membrane-bound IL-6R and has been shown to inhibit both soluble and membrane-bound IL-6R–mediated signaling. IL-6 is a pleiotropic pro-inflammatory multifunctional cytokine produced by a variety of cell types. It has been shown to be involved in diverse physiological processes such as T-cell activation; induction of acute-phase proteins; stimulation of hemopoietic precursor cell growth and differentiation; proliferation of hepatic, dermal, and neural cells; as well as bone metabolism, lipid metabolism, hepatoprotection, and fibrosis. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders including rheumatoid arthritis (RA), Castleman disease, systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA), GCA, Takayasu arteritis (TAK), systemic sclerosis (SSc), and cytokine-release syndrome (CRS).

Inhibition of the biological activity of IL-6 or IL-6R has been effective in the treatment of RA, Castleman disease, sJIA, pJIA, GCA, TAK, and CRS, for which TCZ has been approved in many countries.

TCZ has IV and SC formulations. Both formulations of TCZ have been approved for many of the indications listed above (RA, sJIA, and pJIA), whereas the IV formulation is approved exclusively for Castleman disease and CRS, and the SC formulation is approved exclusively for GCA and TAK. SC TCZ (162 mg once a week [QW] or every 2 weeks [Q2W]) is approved in the European Union, United States, and Japan for the treatment of RA, sJIA, and GCA. SC TCZ is also approved for the treatment of RA in more than 60 additional countries and for the treatment of GCA in 17 additional countries. SC TCZ is also approved in the United States, European Union, Japan, Nicaragua, Bangladesh, and Guatemala for the treatment of pJIA (162 mg Q2W or every 3 weeks). In Japan, SC TCZ has an additional indication for the treatment of TAK (162 mg QW or Q2W).

As of the Development International Birth Date (DIBD) (28 April 1997), an estimated 22,968 patients had received TCZ (IV and SC combined, including blinded TCZ) during clinical trial participation. Cumulatively from the DIBD, 514 patients in clinical trials of special populations have received either IV or SC TCZ (446 pediatric patients and 68 patients of different racial and/or ethnic origins). The combined cumulative postmarketing exposure of patients to IV TCZ is estimated to be 781,084 patients (629,799 patient years [PY]), whereas the combined cumulative postmarketing exposure of patients to SC TCZ is 276,596 patients (226,918 PY).

Refer to the Tocilizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Completed Clinical Studies in Patients with Giant Cell Arteritis

TCZ has been evaluated in two completed randomized controlled trials in patients with GCA. In Study ML25676, 20 patients with GCA received IV TCZ (Villiger et al. 2016). In the Phase III WA28119 (GiACTA) study, 149 patients with GCA received SC TCZ (Stone et al. 2017).

1.2.1.1 Study ML25676: Intravenous Tocilizumab

Study ML25676 was a Phase II, investigator-initiated, single-center, randomized, double-blind study supported by F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) that was conducted at the Inselspital (University Hospital) in Bern, Switzerland. This study evaluated the safety and efficacy of IV TCZ (8 mg/kg) ($n=20$) compared with placebo ($n=10$) in the induction and maintenance of disease remission in patients with newly diagnosed or relapsing GCA (Villiger et al. 2016). Patients in both groups received oral prednisolone, starting at 1 mg/kg/day and tapered down to 0 mg during the study. A significantly higher proportion of patients in the TCZ group reached complete remission at a prednisolone dose of 0.1 mg/kg/day at Week 12 compared with the placebo group (85% vs. 40%, respectively; risk difference = 45%; 95% CI: 11, 79; $p=0.0301$). The proportion of patients who achieved relapse-free survival by Week 52 was also significantly higher in the TCZ group than the placebo group (85% vs. 20%; risk difference = 65%; 95% CI: 36, 94; $p=0.0010$). Importantly, the cumulative dose of prednisolone was significantly lower in patients treated with TCZ (43 mg/kg in the TCZ group vs. 110 mg/kg in the placebo group after 52 weeks; $p=0.0005$).

The safety profile of TCZ was comparable with the established TCZ safety profile with no new safety signal observed. Serious adverse events were observed in 7 patients (35%) in the TCZ group and 5 patients (50%) in the placebo group.

1.2.1.2 Study WA28119: Subcutaneous Tocilizumab

Study WA28119 was a Phase III, randomized, double-blind, placebo-controlled trial of SC TCZ in patients with GCA. The study was composed of a 52-week blinded period followed by a 104-week open-label period. Patients ($n=251$) were randomized in a 2:1:1:1 ratio to receive 162 mg TCZ SC QW or Q2W combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. Sustained remission at Week 52 was achieved in significantly more patients in the TCZ groups than the placebo groups (56% of patients in the TCZ QW group and 53% of patients in the TCZ Q2W group vs. 14% in the placebo group that underwent the 26-week prednisone taper and 18% in the placebo group that underwent the 52-week prednisone taper; $p<0.001$ for either TCZ group vs. placebo). The cumulative mean prednisone dose over the 52-week period was significantly lower in the TCZ groups compared with placebo groups (1862 mg in each TCZ group vs. 3296 mg in the placebo group that underwent the 26-week taper [$p<0.001$ for both comparisons] and vs. 3813 mg in the placebo group that underwent the 52-week taper [$p<0.001$ for both comparisons]).

Up to Week 52, serious adverse events were observed in 15% of patients in the TCZ QW group, 14% of patients in the TCZ Q2W group, and 22% and 25% of patients in the placebo groups who underwent the 26-week and 52-week prednisone tapers, respectively. The open-label part of the study has been completed and the results will be available in 2019.

1.2.2 Pharmacokinetics of Tocilizumab

The pharmacokinetics of TCZ were characterized using non-linear elimination, which is a combination of linear clearance and Michaelis-Menten elimination. The non-linear part of TCZ elimination leads to an increase in exposure that is more than dose-proportional. The total clearance of TCZ is concentration dependent and equals the sum of linear clearance and non-linear clearance. The concentration-dependent non-linear clearance plays a major role at low TCZ concentrations. Once the non-linear clearance pathway is saturated, at higher TCZ concentrations, clearance is mainly determined by the linear clearance. Owing to the effects of non-linear clearance, the half-life of TCZ varies with concentration.

The pharmacokinetics of TCZ after SC administration have been characterized in adult patients with GCA. Peak serum concentrations are achieved by approximately 3 days after QW dosing in the patient populations with GCA. Following administration of 162 mg TCZ QW at steady state, the apparent terminal half-life is up to 18.9 days, whereas after 162 mg TCZ Q2W the apparent terminal half-life is up to 7.9 days. Following the 162 mg QW and Q2W regimens, approximately 90% of steady-state exposure was achieved by 17 and 14 weeks, respectively.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

On the basis of the data from the Phase III WA28119 trial, the SC formulation of TCZ was approved for the treatment of GCA in multiple countries worldwide. Although the approval of SC TCZ is a significant step to improve the treatment paradigm for patients with GCA and reduce the burden of glucocorticoid (GC)-associated toxicity, important challenges remain. The availability of the IV formulation will provide another administration option for those patients who prefer IV infusion because of needle phobia. There is also a significant unmet medical need owing to a patient access issue to TCZ SC under U.S. medical insurance, which would not apply to TCZ IV. Furthermore, the patient population with GCA is older than the patient population with RA, and an unmet medical need exists for a subset of this elderly population for whom the IV infusion will be preferable, as some patients may either have difficulty administering the SC injections and/or may have suboptimal adherence to SC treatment.

Based on the extensive safety data in the RA program and GCA studies, the adverse effects of TCZ have been shown to be manageable, reversible, and usually not treatment limiting. Furthermore, the results of Study ML25676 described previously

(see Section 1.2.1.1) indicate a positive benefit–risk profile for the IV route of administration of TCZ in GCA similar to that observed for the approved SC route.

Although Study ML25676 was conducted evaluating the 8 mg/kg IV dose every 4 weeks (Q4W) regimen and observed trough exposures were within the therapeutic range established in Study WA28119, model based predictions show that average exposures (area under the concentration–time curve [AUC]), but not peak concentrations), over a dosing interval at steady state are higher than those observed in the RA population at the same dose. Average steady-state concentration at the end of a dosing interval (C_{trough}) exposure in patients with GCA from the SC QW regimen (n = 100), SC Q2W regimen (n = 49), or 8 mg/kg IV (Q4W) regimen (n = 9) were higher than C_{trough} from corresponding doses in patients with RA (67.93 vs. 44.17 μg/mL, 12.2 vs. 8.23 μg/mL, and 36.9 vs. 21.1 μg/mL, respectively; (Clinical Study Reports [CSRs] WA28119 and ML25676). Thus, at the same dose, patients with GCA have higher exposure by approximately 50% than patients with RA.

Although a post-hoc analysis of the pharmacokinetics of TCZ was undertaken using samples collected during Study ML25676, the data are sparse. Therefore, in order to supplement the pharmacokinetic (PK) data collected in this study and to identify the optimal dose of IV TCZ that will best match the exposure leading to efficacy after SC TCZ administration as observed in Study WA28119, this study will examine exposures achieved at steady state from multiple doses of 6 and 7 mg/kg IV TCZ Q4W (see Section 3.3.1 for the rationale for selection of TCZ dose and schedule).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, pharmacodynamics, and safety of 6 and 7 mg/kg of TCZ administered by IV infusion Q4W to patients with GCA. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PHARMACOKINETIC OBJECTIVES

The primary PK objective for this study is to characterize the pharmacokinetics of two dose levels of TCZ administered by IV infusion to patients with GCA, on the basis of the following endpoints:

- Steady-state maximum serum concentration (C_{max}) at specified timepoints
- C_{trough} at specified timepoints
- AUC over the dosing interval of 4 weeks (AUC_{4weeks}) at specified timepoints

2.2 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic (PD) objective for this study is to assess the pharmacodynamics of two dose levels of TCZ administered by IV infusion to patients with on the basis of the following endpoints:

- Serum concentration of IL-6 at specified timepoints

- Serum concentration of sIL-6R at specified timepoints
- Serum concentration of C-reactive protein (CRP) at specified timepoints
- Erythrocyte sedimentation rate (ESR) at specified timepoints

2.3 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of two dose levels of TCZ administered by IV infusion to patients with GCA on the basis of the following endpoints:

- Nature, frequency, severity, and causality of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Clinical safety laboratory results

2.4 EXPLORATORY OBJECTIVE

The exploratory objective for this study is to monitor the efficacy of two dose levels of TCZ administered by IV infusion to patients with GCA on the basis of the following endpoints:

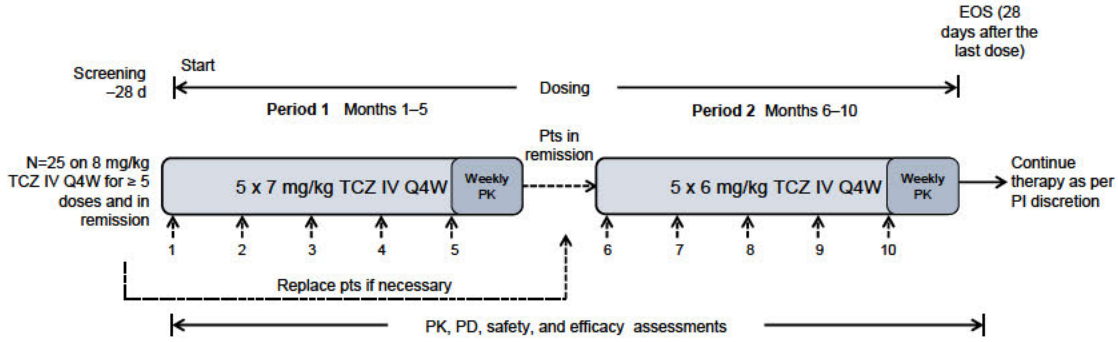
- Proportion of patients who experience a flare, defined as the recurrence of signs or symptoms of GCA and/or ESR $\geq$30 mm/h attributable to GCA as determined by the investigator, during each period
- Proportion of patients in remission, defined as the absence of flare (defined above) and normalization of CRP ($<$1 mg/dL), at each visit

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib, open-label, dose-ranging study designed to characterize the pharmacokinetics, pharmacodynamics, and safety of two dose levels of TCZ (6 and 7 mg/kg) administered by IV infusion Q4W to patients with GCA. This study will enroll patients with GCA from at least two sites in Switzerland who have received at least five consecutive doses of 8 mg/kg TCZ IV Q4W prior to baseline in clinical practice and who have reached remission (defined in Section 2.4). An overview of the study design is shown in Figure 1. A schedule of activities is provided in Appendix 1, and the schedule for PK and IL-6/sIL-6R sample collection is presented in Appendix 2.

Figure 1 Study Schema



EOS = end of study; PD=pharmacodynamic; PI =Principal Investigator; PK=pharmacokinetic; pts=patients; Q4W=every 4 weeks; TCZ=tocilizumab.
Note: Vertical arrows indicate TCZ administration and numbers denote the dose number.

The study is divided into two periods: In Period 1, approximately 25 patients who have been receiving 8 mg/kg TCZ IV Q4W for a minimum of five consecutive doses and who are in remission will receive five consecutive doses of 7 mg/kg TCZ IV Q4W. Subsequently, if a patient is still in remission at the end of Period 1, the patient will enter Period 2 and receive five consecutive doses of 6 mg/kg TCZ IV Q4W. Although five doses at each dose level are sufficient to achieve the primary study objectives, if absolutely necessary to accommodate patient availability for the intensive PK sampling during the last dosing cycle, the dosing periods may be extended by one dose for a total of six doses. This will not be considered a protocol violation.

The plan is to enroll approximately 25 patients into Period 1 in order to obtain data to robustly characterize the pharmacokinetics at each of the two dose levels. Guidance from a statistical evaluation of the variability in PK parameters from IV dosing (see Section 6.1) established a minimum of 12 patients would be adequate. Given the open-label nature of the study design, an evaluation of the data at the end of Period 1 will be undertaken. If the dropout rate and/or variability are higher than planned, additional patients on 8 mg/kg TCZ IV Q4W (who have received at least five consecutive doses and are in remission) may be directly enrolled into Period 2. Because the study design allows sufficient time to achieve steady state at the 6 mg/kg dose level, there is minimal influence from the small difference expected in PK and PD outcomes from prior dosing with 8 mg/kg versus 7 mg/kg; hence the protocol allows for direct enrollment of patients who had received either 8 mg/kg or 7 mg/kg TCZ IV Q4W into Period 2. Data from all patients receiving 6 mg/kg TCZ IV Q4W in Period 2 will be combined.

PK samples will be obtained before and after each infusion of TCZ to characterize the C_{max} and C_{trough} of TCZ, and more intensive sampling during the last dosing cycle will be used to estimate the steady-state AUC_{4weeks} at each dose level.

The usage of GC during the study is at the discretion of the investigator. Only patients in remission at the end of Period 1 will be eligible for Period 2.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs, which corresponds to approximately 28 days after the last dose. The end of the study is expected to be approximately 10 months after enrollment of the last patient into Period 1.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 12 months.

In addition, the Sponsor may decide to terminate the study at any time.

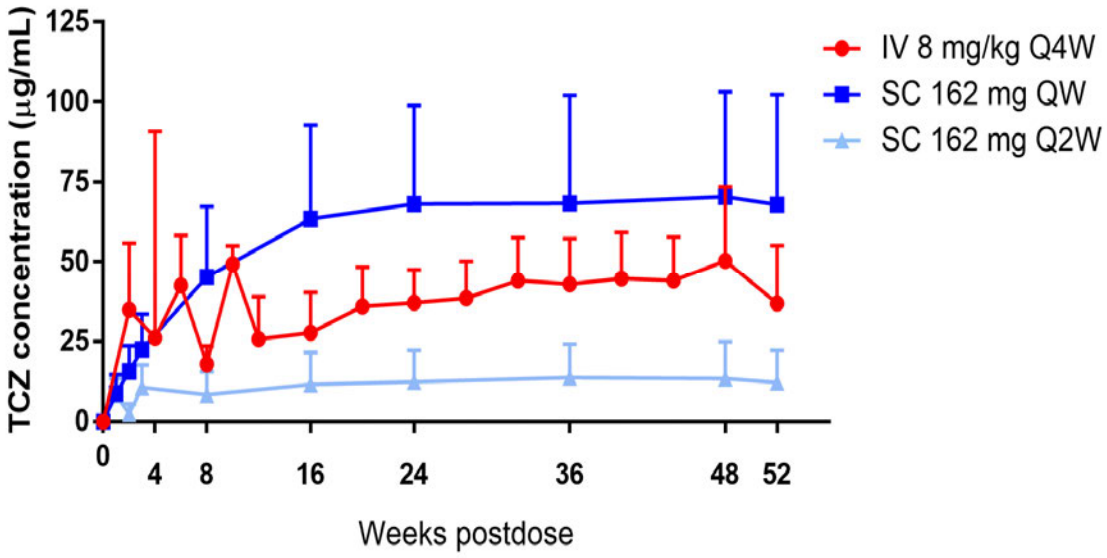
3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Selection of Tocilizumab Dose and Schedule

The study is designed to robustly characterize the steady-state pharmacokinetics of TCZ in patients with GCA at two IV administration dose levels and compare with the previously characterized pharmacokinetics of TCZ in the GCA population after SC administration and in the RA population after IV administration. The first dose of 7 mg/kg TCZ IV Q4W was selected on the basis of 1) the cumulative knowledge of the concentration of TCZ required to saturate the target IL-6R; 2) the therapeutic levels established in Study WA28119, in which TCZ was administered to patients with GCA at doses of 162 mg SC QW or Q2W; 3) the C_{trough} measured in Study ML25676, in which TCZ was administered to patients with GCA at a dose of 8 mg/kg IV Q4W; and 4) the exposure (AUC and C_{max}) of TCZ in patients with RA based on a large global database of multiple Phase III trials (Frey et al. 2010; Abdallah et al. 2017).

The safety of the 8-mg/kg TCZ IV Q4W dosing regimen has been well established in the RA population for which TCZ has been approved for 9 years in the European Union and 8 years in the United States. C_{trough} after IV administration in Study ML25676 was estimated to be within the range of the C_{trough} in Study WA28119 (see Figure 2). Results from Study ML25676 indicated that the 8 mg/kg TCZ IV Q4W dosing regimen was efficacious and no new safety signals were identified. A combined population (pop)-PK model was developed based on data from both SC and IV doses of TCZ in patients with GCA. The model revealed that clearance at steady state in patients with GCA is lower than in patients with RA. The exact cause for this is unknown. This difference leads to a predicted 50% higher AUC, with no resultant effect on C_{max}. Because of this difference, the AUC or average trough concentration ($C_{average}$) in patients with GCA is anticipated to be higher than in patients with RA.

Figure 2 Observed Serum TCZ Concentration Profile of the 8 mg/kg IV Q4W (ML25676), 162 mg SC QW, and 162 mg SC Q2W Doses (WA28119) in Patients with GCA



GCA = giant cell arteritis; Q2W = every 2 weeks; Q4W = every 4 weeks; QW = once a week; TCZ = tocilizumab.

Simulations were conducted to estimate doses lower than 8 mg/kg that could be expected to deliver sufficient TCZ exposures to ensure efficacy in GCA patients (i.e., a C_{trough} in between that achieved with 162 mg TCZ SC QW and Q2W in WA28119) with an overall exposure (C_{max}, AUC) more comparable to that achieved in adult patients with RA.

A large database exists from the Phase III studies in patients with RA, which provides evidence of a positive benefit–risk assessment at these exposures. Thus, it is anticipated that a TCZ regimen of 6 or 7 mg/kg Q4W will result in drug exposures that are efficacious and well tolerated in the GCA population. A further decrease in dose level to 4 mg/kg TCZ IV Q4W was not considered adequate given it is predicted to result in a C_{trough} below that of 162 mg SC Q2W in patients with GCA (Table 1).

Table 1 Median (Range) Population PK Model–Estimated TCZ Exposures in GCA versus RA by SC and IV Regimens

Treatment Arm	n	AUC_{4weeks} (μg/mL × day)	C_{mean} (μg/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)
GCA [a]					
162 mg SC QW	100	1988 (324–4188)	71.0 (11.6–145)	72.5 (12.1–152)	67.6 (10.6–145)
162 mg SC Q2W	49	387 (15.2–1375)	13.8 (0.5–49.1)	17.4 (1.1–56.5)	7.8 (0.1–37.3)
8 mg/kg IV Q4W	15	2304 (1714–3373)	82.3 (61.2–121)	174 (134–239)	39.5 (24–72.2)
7 mg/kg IV Q4W [b]	15	1831 (1308–2731)	65.4 (46.7–97.5)	145 (109–203)	28.0 (14.5–55.3)
6 mg/kg IV Q4W [b]	15	1362 (918–2111)	48.6 (32.8–75.4)	117 (84–167)	16.6 (5.4–38.4)
RA [c]					
162 mg SC QW	621	1325 (68–4114)	47.3 (2.4–147)	49.8 (3–149.6)	42.9 (1.3–143.6)
162 mg SC Q2W	509	256 (6–1221)	9.2 (0.2–43.6)	12.1 (0.4–49.3)	4.1 (0.0–34.2)
8 mg/kg IV Q4W	2155	1512 (476–7283)	54.0 (17–260)	176 (75.4–557)	13.4 (0.1–154)
4 mg/kg IV Q4W	267	504.5 (249–1419)	18.0 (8.9–50.7)	86.1 (44.8–202)	0.1 (0.0–14.6)

AUC_{4weeks}=area under the concentration–time curve over 4 weeks (the dosing interval); C_{max}=maximum serum concentration; C_{mean}=mean serum concentration; C_{trough}=(minimum serum) trough concentration; GCA=giant cell arteritis; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; RA=rheumatoid arthritis.

[a] Source: GCA SC and GCA IV (Report 1085349).

[b] Model simulated for the population in Study ML25676.

[c] Source: RA (Report 1073817).

Simulations were also conducted to estimate the time required to achieve steady state at both dose levels under the conditions of the study. It is anticipated that five doses of 7 mg/kg TCZ IV Q4W in patients who are already receiving the 8 mg/kg Q4W regimen at study entry will be sufficient to characterize steady-state C_{trough} and C_{max}. Following five doses of 7 mg/kg TCZ IV Q4W, five doses of 6 mg/kg TCZ IV Q4W will be sufficient to characterize steady-state exposure parameters at this lower dose level. Thus, under the conditions of this study, the observed steady-state C_{trough}, C_{max}, and AUC_{4weeks} will be characterized at both doses. Simulations also show that 28 days after the last dose corresponds to approximately 2 half-lives at the concentrations achieved from both doses.

Because overall exposures from 6 and 7 mg/kg TCZ IV Q4W are expected to be similar to levels previously established as safe, no new safety findings are anticipated.

Because C_{trough} is expected to be within the therapeutic range from both doses, efficacy is anticipated to be maintained. PK data from this study will be used to robustly characterize the trough, peak, and average concentrations of TCZ by IV administration in patients with GCA. This, along with efficacy, safety, and PK results collected in Studies ML25676 and WA28119, will inform the selection of an optimal IV TCZ dose for the treatment of GCA.

3.3.2 Rationale for Patient Population

This study will enroll patients with GCA who are already receiving IV TCZ therapy in clinical practice at two sites in Switzerland. Patients who are already receiving stable IV TCZ therapy in clinical practice may have a preference for IV treatment and thus are likely to continue their participation in the trial while maintaining disease control. Eligible patients with GCA must have been receiving TCZ 8 mg/kg IV Q4W for at least five consecutive doses and be in remission (defined in Section 2.4). Patients entering Period 2 of the study (see Section 3.1) must be in remission prior to the first dose of TCZ 6 mg/kg IV.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll approximately 25 adult patients with a diagnosis of GCA who are being treated with 8 mg/kg TCZ IV Q4W in clinical practice and have reached remission at the time of enrollment.

4.1.1 Inclusion Criteria

Patients entering Period 1 or Period 2 directly (without prior participation in Period 1) must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 50 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of GCA classified according to the following criteria:
  - Age ≥ 50 years
  - History of ESR ≥ 50 mm/hour *

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

  AND at least one of the following:

  - Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

- Symptoms of polymyalgia rheumatica (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

AND at least one of the following:

- Temporal artery biopsy revealing features of GCA
- Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), or positron emission tomography-computed tomography (PET-CT)

- For patients entering Period 1: patients must be receiving treatment with TCZ 8 mg/kg IV Q4W and have received at least five consecutive doses prior to baseline and be in remission (as defined in Section 2.4) at baseline.
- For patients entering Period 2 after completing Period 1: prior to the first dose of 6 mg/kg TCZ IV, patients must be in remission (as defined in Section 2.4) at the end of Period 1.
- For patients entering Period 2 directly (without prior participation in Period 1): patients must be receiving treatment with TCZ 8 mg/kg IV Q4W and have received at least five consecutive doses prior to the first study visit in Period 2 and be in remission (as defined in Section 2.4) at the first study visit in Period 2.
- For women: not of childbearing potential. A woman is considered to be not of childbearing potential if she has reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause) or has undergone surgical sterilization (removal of ovaries and/or uterus). The definition of non-childbearing potential may be adapted for alignment with local guidelines or requirements.
- For men: not of reproductive potential (i.e., infertile or sterilized) or agreement to use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must use a condom during the treatment period and for at least 28 days after the final dose of TCZ. Men must refrain from donating sperm during this same period.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Lack of peripheral venous access
- Major surgery within 8 weeks prior to screening, or planned major surgery during the study
- Organ transplant (except corneal transplant performed more than 3 months prior to screening)
- Major ischemic event, related or unrelated to GCA, within 12 weeks prior to screening

- Treatment with any other investigational agent besides TCZ within 12 weeks (or 5 half-lives of the investigational drug, whichever is longer) prior to screening
- Previous treatment with cell-depleting therapies, including investigational agents, including, but not limited to, Campath® (alemtuzumab), anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20
- Treatment with IV gamma globulin or plasmapheresis within 6 months prior to baseline (Day 1)
- Previous treatment with alkylating agents, such as chlorambucil, or with total lymphoid irradiation
- Immunization with a live or attenuated vaccine within 4 weeks prior to baseline
- Treatment with hydroxychloroquine, cyclosporine A, azathioprine, or mycophenolate mofetil within 4 weeks prior to baseline (Day 1)
- Treatment with other biologics (e.g., etanercept, infliximab, certolizumab, golimumab, abatacept, adalimumab, anakinra) or targeted synthetic disease-modifying anti-rheumatic drug (e.g., tofacitinib, baricitinib) within 12 weeks prior to baseline (Day 1)
- Treatment with cyclophosphamide within 6 months of baseline (Day 1)
- History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies (including history of discontinuation of TCZ due to any infusion-related reaction or hypersensitivity)
- Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), psychiatric, osteoporosis or osteomalacia, glaucoma, corneal ulcers or injuries, or gastrointestinal (GI) disease
- Current liver disease, as determined by the investigator
- History of diverticulitis, diverticulosis requiring antibiotic treatment, or chronic ulcerative lower GI disease such as Crohn disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose a patient to perforations
- Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including, but not limited to, tuberculosis [TB] and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of the nail beds)
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks of screening
- Active TB requiring treatment within the previous 3 years

  Patients should be screened for latent TB and, if positive, treated according to local practice guidelines prior to baseline (see Appendix 3).

  Patients treated for TB with no recurrence within the last 3 years and patients treated for latent TB within the last 3 years are eligible.
- Primary or secondary immunodeficiency (history of or currently active)

- Evidence of malignant disease or malignancies diagnosed within the previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that have been excised and cured)
- History of alcohol, drug, or chemical abuse within 1 year prior to screening
- Body weight $>$ 150 kg

At screening:

- Serum creatinine $>$ 1.4 mg/dL (124 μmol/L) in female patients and $>$ 1.6 mg/dL (141 μmol/L) in male patients
- ALT or AST $>$ 1.5 $\times$ upper limit of normal (ULN)
- Total bilirubin $>$ ULN
- Platelet count $< 100 \times 10^9$/L (100,000/mm^3)
- Hemoglobin $<$ 85 g/L (8.5 g/dL; 5.3 mmol/L)
- WBCs $< 3.0 \times 10^9$/L (3000/mm^3)
- ANC $< 1.5 \times 10^9$/L (*1500*/mm^3)
- Absolute lymphocyte count $< 0.5 \times 10^9$/L (500/mm^3)
- Positive hepatitis B surface antigen (HBsAg) test or positive hepatitis C antibody test

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a single-arm and open-label study with no randomization. The primary PK objective of this study is to characterize the pharmacokinetics of TCZ by IV administration in patients with GCA. To fulfill this objective, the use of a blind or a comparator arm is not necessary.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is TCZ.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Tocilizumab

TCZ will be supplied by the Sponsor as a sterile IV injection for reconstitution in 20-mL glass vials with a 10 mL fill in each (200 mg /10 mL of TCZ). An appropriate number of vials (depending on the patient's bodyweight) of TCZ will be assigned to each patient for each infusion to be administered every 28 ($\pm$ 3) days. The amount of solution that is withdrawn from each vial will depend on the patient's allocated dose. For information on the formulation and handling of TCZ, see the TCZ pharmacy manual, Tocilizumab Investigator's Brochure, and Switzerland prescribing information for TCZ.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.

4.3.2.1 Tocilizumab

TCZ will be administered by IV infusion at doses of 7 or 6 mg/kg Q4W. The maximum dose of TCZ that will be administered is 800 mg. The dose of TCZ infusion will be calculated on the basis of body weight measured prior to each infusion (see Appendix 1).

TCZ must be administered under close supervision of the investigator in a setting where medications and resuscitation facilities are available. Patients should be monitored for at least 2 hours after the TCZ infusion is completed.

The TCZ vials will be stored at a temperature of 2°C–8°C. The infusion bag of TCZ may be stored at 2°C–8°C for 24 hours providing that the infusion is prepared aseptically and allowed to return to room temperature before administration. The TCZ will be administered at room temperature by controlled infusion into an arm vein over a 1-hour period. In exceptional cases this time may be extended to up to 6 hours. The infusion speed must be 10 mL/hr for 15 minutes and then increased to 130 mL/hr to complete the dosing in 1 hour. The entire 100 mL-content of the infusion bag must be administered. A total of 20 mL of normal saline will be administered following the infusion of study medication to flush the remaining study drug through the intravenous set.

Refer to the Tocilizumab Investigator's Brochure for further instructions regarding recommended storage conditions and packaging configuration.

4.3.3 Investigational Medicinal Product Accountability

The IMP (TCZ) required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Tocilizumab

The Sponsor does not have any plans to provide the Roche IMP (TCZ) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing TCZ in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY, PROHIBITED THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 28 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- CS's may be used at the discretion of the investigator for the management of patients with refractory GCA or for safety reasons during the study.
- Patients may receive other concomitant medications for GCA or other medical conditions during the study at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., IL-6) during chronic inflammation. Therefore, for molecules that antagonize cytokine activity, such as TCZ, it is expected that the formation of CYP450 enzymes could be normalized. When starting TCZ therapy, patients taking medications that are

individually dose adjusted and metabolized by means of CYP450, CYP3A4, CYP1A2, or CYP2C9 (e.g., atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin, or benzodiazepines) are recommended to be monitored as doses may need to be adjusted to maintain their therapeutic effect. However, because patients in this study will have been treated with TCZ for a minimum of 5 months, it is expected that any effects on the clearance of these drugs would be stabilized by the time of enrollment into this study.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Treatment with any investigational agent, cell-depleting therapies, biologic agents (e.g., tumor necrosis factor antagonists), Janus kinase inhibitors (e.g., tofacitinib, baricitinib), alkylating agents (e.g., chlorambucil, cyclophosphamide), thalidomide, IV gamma globulin, antithymocyte globulin, and azathioprine during the study
- Bone marrow transplantation with total lymphoid irradiation during the study
- Plasmapheresis or extracorporeal photopheresis during the study
- Immunization with a live or attenuated vaccine for the duration of the patient's study participation.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. The schedule for PK and IL-6/sIL-6R biomarker sample collection is presented in Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and last available laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Description of Study Assessments

The sequence of assessments at each visit will be standardized as follows (at visits required in the schedules of assessments).

1. Laboratory samples: All samples (including for predose PK, safety, and efficacy) must be taken prior to study drug treatment, except for postdose samples for PK analyses, which will be obtained after study drug treatment. The laboratory samples should be drawn at least 30 minutes before clinical assessment.
2. Efficacy assessments: signs and symptoms of GCA
3. Safety assessments: review of adverse events, vital signs, concomitant medications
4. IV infusion of TCZ
5. Postdose PK samples (only at scheduled visits)

Schedules of assessments are found in Appendix 1 and Appendix 2.

4.5.3 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases within the past 10 years, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to initiation of study treatment will be recorded. At the time of each visit, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.4 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations may be performed at unscheduled postbaseline visits as clinically indicated. Changes from baseline abnormalities should

be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, patient body weight will be measured at the timepoints specified in the schedule of activities (see Appendix 1).

4.5.5 Vital Signs

Vital signs will include measurements of pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Blood pressure measurements should be obtained prior to the infusion and after the patient has been seated for at least 5 minutes.

4.5.6 Disease-Specific Assessment

Evaluation of clinical signs and symptoms by the investigator at every study visit according to the schedule of assessment will include the following:

- Fever (≥38°C or 100.4°F)
- Symptoms of polymyalgia rheumatica (PMR; morning stiffness and/or pain, in the shoulder and/or hip girdles)
- Localized headache, temporal artery or scalp tenderness
- Visual signs or symptoms such as acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy, transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes)
- Jaw or mouth pain
- New or worsened extremity claudication
- Other features judged by both the clinician-investigator to be consistent with a GCA or PMR flare

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- ESR (using the Westergren method; to be assessed locally using a kit provided by the Sponsor)
- TB screening test (see Appendix 3 for detailed description)

The following samples will be sent to the *Sponsor's designees (as outlined below)* for analysis:

- Serum samples for PK analysis
- Serum samples for immunogenicity analysis (anti-drug antibodies)
- Serum samples for PD assessment of sIL-6R
- Serum samples for PD assessment of IL-6

- CRP (high-sensitivity CRP)
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin (direct and indirect bilirubin will be performed if total bilirubin is greater than the ULN), ALP, ALT, AST, uric acid, CPK, and lactate dehydrogenase
- Viral serology: HBsAg, total hepatitis B core antibody, and hepatitis C virus antibody
- Lipid panel: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides

  Overnight fasting (> 8 hours) is required
- Pregnancy test

  Urine pregnancy tests will be performed at screening and at the end of the study. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination only if indicated after local dipstick analysis (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)

Covance Laboratories will transport and analyze the safety samples collected during the study. Following analysis, any residual from these samples will be destroyed within 7 days. In addition, Covance Laboratories will transport, temporarily store, and then ship PK/PD/anti-drug antibody samples to QPS Netherlands for analysis and storage until the final clinical study report has been written, after which the samples will be destroyed. In the case of positive tests for anti-TCZ antibody, the samples will be sent to SRL, Inc. for IgE testing.

The addresses of the above-mentioned laboratories are provided below:

Covance Laboratories

Covance Central Laboratory Services SA
Rue Moïse-Marcinhes 7
1217 Meyrin/Genève
Switzerland

QPS Netherlands

QPS Netherlands B.V., Sample Team
Professor Rankestraat 42–44
9713 GG Groningen
The Netherlands

SRL, Inc.

SRL, Inc.
Second Hachioji Laboratory
Immuno-chemistry Dept.
51 Komiyacho, Hachioji
Tokyo, 192-8535
Japan

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final CSR has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at screening, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as clinically indicated. At screening, if an ECG has been obtained within the past 6 months that shows no clinically significant abnormality and no signs or symptoms suggestive of cardiovascular disease that would exclude the patient, then an additional ECG is not required.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.9 Chest X-rays

Posterior–anterior and lateral chest X-rays (or chest X-rays in accordance with local requirements) should be obtained at screening and reviewed by the investigator or his or her designee. At screening, if a chest X-ray has been obtained within the past 6 months that shows no clinically significant abnormality and no signs or symptoms suggestive of pulmonary disease that would exclude the patient, then an additional chest X-ray is not required.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Any event that meets stopping criteria defined in Section 5.1.1

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment must withdraw from the study and may be replaced.

Patients will return to the clinic for a treatment discontinuation visit 28 (±3) days after the final dose of study drug (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study may be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with TCZ in clinical studies and post-market experience. The important safety risks for TCZ are outlined below. Please refer to the Tocilizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events and laboratory abnormalities, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Tocilizumab

5.1.1.1 Hypersensitivity Reactions, Including Anaphylaxis

An infusion reaction is defined as any adverse event that occurs during or within 24 hours after the infusion. This may include hypersensitivity or anaphylactic reactions. Stevens-Johnson syndrome has been reported during treatment with TCZ in the post-marketing setting. Signs of a possible hypersensitivity reaction include, but are not limited to, the following:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension

TCZ infusions will be administered to patients at the site under close supervision. Health care professionals administering TCZ infusions should be trained in the appropriate procedures for TCZ administration, should be able to recognize the symptoms associated with potential hypersensitivity reactions, including anaphylaxis, and should have the appropriate medication available for immediate use in case of hypersensitivity reaction such as anaphylaxis during or after administration of TCZ. The patient should be treated according to the standard of care for management of the hypersensitivity reaction.

Study site personnel should educate patients about the signs and symptoms of hypersensitivity and anaphylaxis and instruct them to seek medical attention if they experience symptoms of a hypersensitivity reaction outside of the clinic. Patients enrolled in this study will be provided with a Patient Information Card that contains this information.

If a patient has symptoms of serious hypersensitivity reactions, such as anaphylaxis, or requires an interruption of the study drug because of symptoms of hypersensitivity including anaphylaxis, administration of TCZ must be discontinued permanently and the patient should be withdrawn from the study.

For any patients withdrawing from the study because of a serious or non-serious hypersensitivity reaction, including anaphylaxis, blood samples for the presence of anti-TCZ antibodies and PK/PD assessments should be obtained at the time of the event and approximately 8 weeks after the last dose.

5.1.1.2 Serious Infections and Opportunistic Infections

Physicians should exercise caution when considering the use of TCZ in patients with increased risk of infection, such as a history of recurring infections or with underlying conditions (e.g., diabetes mellitus) which may predispose patients to serious infections and opportunistic infections such as TB and viral reactivations (e.g., hepatitis B virus).

Vigilance for timely detection of serious infection is recommended for patients receiving biologic agents, as signs and symptoms of acute inflammation may be lessened

because of suppression of the acute-phase reaction. The effects of TCZ on CRP and neutrophils, and the signs and symptoms of infection, should be considered when evaluating a patient for a potential infection.

Patients enrolled in this study will be provided with a Patient Information Card informing them and health care providers of the importance of recognition of early signs of infections so that appropriate diagnostic and therapeutic measures can be introduced in a timely manner. Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear to ensure rapid evaluation and appropriate treatment.

If a patient develops a serious infection, administration of TCZ should be interrupted until the infection is controlled; therefore, the patient will be discontinued from the study. The investigator should consider the benefits and risks to the patient before resuming treatment with TCZ.

5.1.1.3 Gastrointestinal Perforations

Symptomatic diverticulosis, diverticulitis, or chronic ulcerative lower GI disease, such as Crohn disease, ulcerative colitis, or other chronic lower GI conditions, might predispose patients to GI perforations. Therefore, patients with these conditions are excluded from the study (see Section 4.1.2).

Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticular disease and thus reduce the risk of GI perforations. Therefore, patients should be made aware of the symptomatology suggestive of diverticular disease and be instructed to alert their health care provider as soon as possible if these symptoms arise.

Discontinuation of TCZ is required for patients who develop GI perforations.

5.1.1.4 Hematologic Abnormalities

Decreases in neutrophil and platelet counts, and fibrinogen levels, have been observed following treatment with TCZ. Because the primary objective of the study is to characterize the PK parameters following 7 or 6 mg/kg TCZ IV Q4W, any deviation from the predefined study dose regimen will lead to study withdrawal.

Risk mitigation strategies for neutropenia and thrombocytopenia are summarized in Table 2 and Table 3, respectively.

Table 2 Risk Mitigation for Neutropenia

Laboratory Value	Action
ANC ≤ 1 cell $\times 10^9$/L	Withdraw the patient from the study

Patients withdrawn from the study because of a reduced ANC must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, and must have a repeat WBC count with differential count performed weekly until the ANC is >1 cell $\times 10^9$/L. If the ANC does not return to >1 cell $\times 10^9$/L within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

Table 3 Risk Mitigation for Thrombocytopenia

Laboratory Value	Action
Platelet count $\leq$100 cells $\times 10^3/\mu$L	Withdraw the patient from the study

Patients withdrawn from the study because of a reduced platelet count must repeat platelet tests weekly until the count is $>100{,}000/\mu$L. If platelets do not return to $>100{,}000/\mu$L within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

5.1.1.5 Demyelinating Disorders

The effect of treatment with TCZ on demyelinating disorders is not known; events have been reported rarely. Physicians should exercise caution when considering the use of TCZ in patients with preexisting or recent-onset demyelinating disorders.

Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. During assessment of a potential demyelination event, treatment with TCZ should be interrupted and patients will be discontinued from the study.

5.1.1.6 Elevated Liver Enzymes

Risk mitigation strategies for patients with elevated ALT or AST are presented in Table 4. Because the primary objective of the study is to characterize the PK parameters following administration of 7 or 6 mg/kg TCZ IV Q4W, any deviation from the predefined study dose regimen will lead to patient withdrawal from the study.

Table 4 Risk Mitigation for Liver Enzyme Abnormalities

ALT or AST Values	Action
Greater than 1 to 3 × ULN [a]	*Modify the dose of concomitant MTX if appropriate.* For persistent increases (e.g., at least two consecutive measurements) in this range, withdraw the patient from the study.
Greater than 3 × ULN [a] (confirmed by repeat testing)	Withdraw the patient from the study.

MTX = methotrexate; ULN = upper limit of normal.

[a] ULN or the patient's baseline value, whichever is higher

The Medical Monitor should be contacted for further discussion of the case if ALT or AST elevation > 3 × ULN is combined with at least one of the following:

- Total bilirubin > 2 × ULN
- INR > 1.5
- ALP > 2 × ULN
- Presence of worsening fatigue, nausea, vomiting, fever, rash, or eosinophilia

Patients who are withdrawn from the study because of elevated liver function tests must have repeat tests performed as clinically indicated until levels return to baseline. If the patient's liver function tests have not returned to normal or the patient's baseline level within 6 months (or sooner if deemed necessary by the investigator), the investigator should consider referral to a specialist. If the specialist deems a liver biopsy necessary, the prepared histologic slides will be requested by the Sponsor for central review by a third party, and the biopsy report should be forwarded to the Sponsor.

5.1.1.7 Elevated Lipids

Patients with GCA are at increased risk for cardiovascular disorders; therefore, risk factors for cardiovascular disease should be managed as part of standard of care.

For patients with LDL cholesterol levels of ≥ 160 mg/dL, it is strongly recommended that investigators advise therapeutic lifestyle changes that may include initiation of lipid-lowering agents. Lipid-lowering agents should also be considered for patients with lower LDL cholesterol levels as part of their therapeutic lifestyle changes, depending on their overall risk as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (NCEP 2002) or other national guidelines.

5.1.1.8 Malignancies

The effect of IL-6R signaling inhibition on the development of malignancies is not known. Although no imbalance of malignancies was observed in controlled clinical trials of TCZ

in patients with RA, malignancies have been identified as a concern for other biologic agents. It is recognized that, given the latency for such events, identification of malignancies in TCZ-treated patients may require a longer period of surveillance. TCZ administration should be discontinued for patients with malignancies (with the exception of local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured).

5.1.1.9 Immunogenicity

Serious hypersensitivity reactions (i.e., clinically significant infusion reactions or anaphylaxis), and lack of efficacy or decreased efficacy, are potential risks that could be associated with development of anti-TCZ antibodies.

Because the patients recruited in the study have been previously treated with TCZ, the immunogenicity assessment in this study will be "event-driven." A sample will be taken prior to the first study dose at baseline or the first visit at Period 2 for those patients entering Period 2 directly. For any patients withdrawing from the study because of serious or non-serious hypersensitivity reaction, including anaphylaxis, blood samples for the presence of anti-TCZ antibodies and PK/PD assessments should be obtained at the time of occurrence of the event and approximately 8 weeks after the last dose, as outlined in Appendix 1.

5.1.1.10 CYP450 Enzyme Normalization

The expression of hepatic cytochrome P450 (CYP450) enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. TCZ normalizes expression of these enzymes. The effect of TCZ on CYP450 enzymes (except CYP2C19 and CYP2D6) is clinically relevant for CYP450 substrates with a narrow therapeutic index and/or when the dose is individually adjusted.

When starting or stopping therapy with TCZ, patients taking medicinal products which are individually dose adjusted and are metabolized via CYP450 CYP3A4, CYP1A2, CYP2B6, or CYP2C9 (e.g., atorvastatin, calcium- channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, cyclosporine, or benzodiazepines) should be monitored as doses of these products may need to be adjusted to maintain their therapeutic effect.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Serious and/or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Anaphylaxis or hypersensitivity reactions
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events
- Demyelinating disorders

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only the diagnosis of liver failure or hepatitis rather than symptoms like jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of GCA.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of giant cell arteritis, “giant cell arteritis progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Giant Cell Arteritis

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. The determination of clinical progression will be based on investigator's assessment at every visit. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Accidental overdoses or medication errors (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB) or Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D.

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the

Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For TCZ, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with TCZ, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Tocilizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Given the small sample size, the short duration of the study, and open-label design without a control arm, a dose-related effect on flares is not expected to be observed. Sample size estimates are entirely based on PK data. PK, PD, safety, and efficacy data will be summarized descriptively. No formal statistical hypothesis testing is planned. A database lock will occur when the last patient has completed the final visit 28 days after the final dose.

The primary PK variables in this study are estimates of steady-state C_{trough}, C_{max}, and AUC_{4weeks} at the two dose levels of TCZ IV therapy (7 mg/kg Q4W and 6 mg/kg Q4W). For each dose level, C_{trough} and C_{max} will be summarized at each timepoint for each dose administered and AUC_{4weeks} estimated for the last dosing cycle will be summarized as geometric means, medians, ranges, and standard deviations.

6.1 DETERMINATION OF SAMPLE SIZE

In order to provide a precise characterization of PK parameters (C_{trough}, C_{max}, and AUC_{4weeks}), in this study, a hybrid of two approaches will be followed. The first of these approaches is the guidance for estimation of sample size in pediatric studies, which requires a study to be prospectively powered to target 95% CI within 60%−140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric sub-group with at least 80% power (Wang et al. 2012). The second is the sample size guidance from the Food and Drug Administration (FDA) for bioequivalence studies, which specifies the 90% CI for the geometric mean ratio (GMR) should fall within 80%−125% of the GMR estimate (U.S. FDA 2001).

Given the need to characterize the PK parameters to a higher precision than in a pediatric population, the sample size for this study was estimated based on achieving a target of 95% CI for estimates of C_{max} and C_{trough} at each dose level that would fall within 80%−125% of the geometric mean estimate.

In Study ML25676, observed steady-state C_{trough} data were available for 18 patients receiving 8 mg/kg TCZ IV Q4W. The geometric mean was 44.4 μg/mL (95% CI: 37.0, 53.4), with the 95% CI corresponding to 83% and 120% of the geometric mean estimate.

Using the variability in observed steady-state C_{trough} in Study ML25676, a sample size of $n = 17$ will provide $> 80\%$ power to characterize the geometric mean estimate of the

observed C_{trough} and C_{max} so that the 95% CI falls within 80%−125% of the geometric mean estimate of the corresponding PK parameter. A minimal sample size of $n = 12$ would provide $> 80\%$ power for the 90% CI to fall within 80%–125% of the geometric mean estimate of the corresponding PK parameter. To account for potential study dropouts, approximately 25 patients already receiving 8 mg/kg IV TCZ and in remission will be enrolled in the Period 1 of this study with the goal of obtaining robust PK characterization at both dose levels.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete each study period and the study overall will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. The number of doses received will be summarized for each study period. A listing of patients in each period detailing dosing of TCZ will be prepared.

6.3 SUMMARIES OF BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, body weight) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

Medical history data, including surgeries, procedures, and baseline conditions, will be summarized descriptively using the safety population. Previous and concomitant treatment will be summarized descriptively.

6.4 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients who have received one dose of TCZ and have one valid PK sample, with patients grouped according to treatment received.

Individual and mean serum TCZ concentration versus time data will be tabulated and plotted by dose level. The serum pharmacokinetics of TCZ will be summarized by estimating total exposure (AUC_{4weeks}), C_{max}, and C_{trough} at steady state. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter-patient variability and drug accumulation will be evaluated. Additional PK analyses will be conducted as appropriate.

6.5 PHARMACODYNAMIC ANALYSES

The PD analysis population will be identical to the safety analysis population.

Individual and mean serum concentration versus time data will be tabulated and plotted by dose level. CRP and ESR data will be summarized as median and ranges. Estimates for CRP levels and ESR at steady state (after the last dose at each dose

level) will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

6.6 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug and had at least one safety assessment.

Safety will be assessed in terms of adverse events (nature, frequency, severity, and causality). Adverse events will be summarized by study period and listed.

Values, along with change from baseline, will be summarized using descriptive statistics for each laboratory test and vital sign parameter. Marked abnormalities will be listed.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

6.7 EXPLORATORY EFFICACY ANALYSES

The analysis population for the efficacy summaries and listings will consist of all patients who received at least one dose of study drug and had at least one efficacy assessment. A summary by study period and supportive listing of the number of patients with flare(s), and the number of patients in remission by visit will be produced.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final

IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site’s study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Two sites in Switzerland will participate to enroll approximately 25 patients.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal

manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Activities

Period	Scrn (D−28 to −1) [a]	Period 1								Period 2									Early WD [b]
Month		1	2	3	4	5				6	7	8	9	10					
Week		1	4	8	12	16	17	18	19	20	24	28	32	36	37	38	39	40 (EOS)	
Day		1	29	57	85	113	120	127	134	141	169	197	225	253	260	267	274	281	
Visit window (days)			±3	±3	± 3	±3	±1	±1	±1	±1	±3	±3	±3	±3	±1	±1	±1	±1	±3
Informed consent [c]	x																		
Demographic data	x																		
Medical history and baseline conditions	x																		
Physical examination [d]	x																		
Vital signs [e]	x	x	x	x	x	x				x	x	x	x	x				x	x
Weight	x	x	x	x	x	x				x	x	x	x	x					
Chest X-ray [f]	x																		
ECG [g]	x																		
Tuberculosis screening [h]	x																		
Hematology [i]	x	x			x					x			x					x	x
Chemistry panel [j]	x	x	x [k]		x					x	x [l]		x					x	x
Viral serology [m]	x																		
Lipid panel [n]		x								x								x	x
Pregnancy test [o]	x																	x	x

Appendix 1: Schedule of Activities

Period	Scrn (D−28 to −1) [a]	Period 1								Period 2									Early WD [b]
Month		1	2	3	4	5				6	7	8	9	10					
Week		1	4	8	12	16	17	18	19	20	24	28	32	36	37	38	39	40 (EOS)	
Day		1	29	57	85	113	120	127	134	141	169	197	225	253	260	267	274	281	
Visit window (days)			±3	±3	± 3	±3	±1	±1	±1	±1	±3	±3	±3	±3	±1	±1	±1	±1	±3
Urinalysis [p]	x									x								x	x
ESR	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IL-6 and sIL-6R		See Appendix 2																	x [q]
TCZ PK		See Appendix 2																	x [q]
Anti-TCZ Ab		x								x [r]									x [q]
Adverse events [s]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical assessment of GCA signs and symptoms	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TCZ administration (7 mg/kg IV)		x	x	x	x	x													
TCZ administration (6 mg/kg IV)										x	x	x	x	x					

Appendix 1: Schedule of Activities

Ab = antibody; BL = baseline; CRP = C-reactive protein; EOS = end of study; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; HBcAb = total hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV= hepatitis C virus; IL-6 = interleukin 6; LDH = lactate dehydrogenase; NA = not applicable; sIL-6R = soluble IL-6 receptor; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; Scrn = screening; TCZ = tocilizumab; ULN = upper limit of normal; WD = withdrawal.

Notes: Laboratory samples should be drawn at least 30 minutes before clinical assessment. If any patients enter Period 2 directly, the Period 1 assessments should be followed with the exception that patients should receive 6 mg/kg TCZ IV instead of 7 mg/kg.

[a] Screening applies to all patients enrolling in Period 1 or directly into Period 2. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients will return to the clinic for a study discontinuation visit at 28 ($\pm$3) days after the final dose of study drug.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 28 days before initiation of study treatment.

[d] Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Limited, symptom-directed physical examinations may be performed at unscheduled post-baseline visits as clinically indicated per the investigator's discretion.

[e] Vital signs include pulse rate, systolic and diastolic blood pressure (after patient has been seated for at least 5 minutes), and temperature.

[f] Not required if a normal chest X-ray has been obtained within 6 months prior to screening.

[g] ECG recordings will be obtained at screening and subsequently as clinically indicated. An ECG is not required if a normal ECG has been obtained within 6 months prior to screening.

[h] Tuberculosis screening will be performed according to local guidance.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin (direct and indirect bilirubin will be performed if total bilirubin is greater than the ULN), ALP, ALT, AST, uric acid, CPK, and LDH.

[k] Chemistry panel at Week 4 only required for patients who had received only five consecutive doses of 8 mg/kg TCZ IV Q4W prior to baseline.

[l] Chemistry panel at Week 24 only required for patients entering Period 2 directly (without prior participation in Period 1) who had received only five consecutive doses of 8 mg/kg TCZ IV Q4W prior to the first study visit in Period 2.

[m] Patients will be screened for HBsAg, total HBcAb, and HCV antibody.

[n] Lipid panel includes total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Patients are required to fast overnight ($>$8 hours).

[o] All women will have a urine pregnancy test at screening and the end of study. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Pregnancy test on freshly voided urine may be performed at any visit at the investigator's discretion.

[p] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination only if indicated after local dipstick analysis (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[q] For any patients withdrawing from the study because of a serious or non-serious hypersensitivity reaction, including anaphylaxis, blood samples for the presence of anti-TCZ antibodies and PK/PD assessments should be obtained at the time of occurrence of the event and approximately 8 weeks after the last dose.

[r] Only applies to patients who enter Period 2 directly, without first participating in Period 1.

[s] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until the end of study/early withdrawal visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (See Section 5.6).

[t] Medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 28 days prior to initiation of study drug until the end of study visit.

Appendix 2
Schedule of Pharmacokinetic, IL-6, and sIL-6R Samples

Study visit (Weeks)	Study Visit (Days)	Timepoint [a]	PK	IL-6 and sIL-6R
Week 1	Day 1	Predose	x	x
		EOI	x	
Week 4	Day 29 (± 3 d)	Predose		
		EOI		
Week 8	Day 57 (± 3 d)	Predose	x	
		EOI	x	
Week 12	Day 85 (± 3 d)	Predose	x	x
		EOI	x	
Week 16	Day 113 (± 3 d)	Predose	x	x
		EOI	x	
Week 17	Day 120 (± 1 d)	At visit	x	
Week 18	Day 127 (± 1 d)	At visit	x	
Week 19	Day 134 (± 1 d)	At visit	x	
Week 20	Day 141 (± 1 d)	Predose	x	x
		EOI	x	
Week 24	Day 169 (± 3 d)	Predose		
		EOI		
Week 28	Day 197 (± 3 d)	Predose	x	
		EOI	x	
Week 32	Day 225 (± 3 d)	Predose	x	x
		EOI	x	
Week 36	Day 253 (± 3 d)	Predose	x	x
		EOI	x	
Week 37	Day 260 (± 1 d)	At visit	x	
Week 38	Day 267 (± 1 d)	At visit	x	
Week 39	Day 274 (± 1 d)	At visit	x	
Week 40 (EOS)	Day 281 (± 1 d)	At visit	x	x

D = day; EOI = end of infusion; IL-6 = interleukin-6; PK = pharmacokinetic; sIL-6R = soluble interleukin-6 receptor.

[a] Predose PK, IL-6, and sIL-6R assessments will be obtained from a single specimen and should be taken 0–3 hours before the start of infusion. EOI samples should be taken 0–15 minutes after the saline flush marking the end of infusion and should be obtained from the patient's opposite arm relative to the dosing arm.

Appendix 3 Tuberculosis Screening and Treatment Assessments

Tuberculosis Screening

Before initiation of therapy with study drug, all patients must be evaluated for both active and inactive (latent) tuberculosis (TB; *Mycobacterium TB* infection). This evaluation may include the following (additional local recommendations may apply):

- Medical history
- Physical examination
- Test for TB infection (TB skin test or special blood test)
- Chest radiograph (X-ray)
- Appropriate bacteriologic or histologic examinations (tests to see whether TB bacteria are in the sputum)

A test for latent TB (per local practice guidelines or as described below) must be performed within 3 weeks prior to the initiation of study drug treatment.

- The Mantoux tuberculin skin test (purified protein derivative [PPD]) and interferon (IFN)-γ–based test (e.g., the QuantiFERON®-TB Gold [QFT-G]) are examples of acceptable screening assays for latent TB in this study.
- An IFN-γ–based test should be considered when the results of the tuberculin skin test are not considered reliable (e.g., positive PPD test in a patient with previous bacille Calmette Guérin vaccination or a negative PPD test in a patient who may be anergic).

All TB testing will be performed locally. Investigators are reminded of the risk of false-negative tuberculin skin test results, especially for patients who are severely ill or immunocompromised.

TB Treatment

If active TB is diagnosed, study drug treatment must not be initiated.

If inactive (latent) TB is diagnosed, appropriate treatment for latent TB must be started with anti-TB prophylaxis therapy 4 weeks before the treatment with study drug is initiated. If a full course of anti-TB treatment for latent TB has been completed previously, there is no need to initiate the treatment again; however, the potential risk of re-infection should be evaluated.

If inactive (latent) TB is suspected, a physician with expertise in the treatment of TB should be consulted. In all situations described below, the benefit–risk balance of therapy should be carefully considered.

Use of anti-TB therapy should also be considered before the initiation of study drug in patients with a history of inactive (latent) or active TB in whom an adequate course of

treatment cannot be confirmed. Some patients who have previously received treatment for inactive (latent) or active TB have developed active TB while being treated with study drug. If an individual is determined to have a positive TB test result based on country-specific guidelines (or U.S. guidelines if none exist), the local country guidelines should be consulted for acceptable anti-TB treatment regimens. If no local guidelines exist for treatment of immunocompromised individuals, then the U.S. guidelines must be followed.

Patients should be instructed to seek medical advice if signs or symptoms (e.g., persistent cough, wasting/weight loss, low-grade fever) suggestive of TB occur during or after therapy with study drug.

The U.S. guideline can be found at the following link: http://www.cdc.gov/tb/.