**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

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# STATISTICAL ANALYSIS PLAN

**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

**STUDY DRUG:** Tocilizumab (RO4877533)

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## STATISTICAL ANALYSIS PLAN APPROVAL

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**Revision History**

| Date | Description |
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| 22-Dec-2020 | • Addition of Pharmacokinetic (PK)-Evaluable population definition<br>• Listing of serious adverse events added as per ICH E3<br>• Addition of Pharmacodynamic analyses by day of steady state<br>• Some minor updates |

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# GLOSSARY OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AESI | Adverse events of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration–time curve |
| $AUC_{4weeks}$ | area under the concentration–time curve over 4 weeks (the dosing interval) |
| BUN | blood urea nitrogen |
| $C_{max}$ | maximum serum concentration |
| $C_{trough}$ | trough concentration |
| CRP | C-reactive protein |
| CPK | creatine phosphokinase |
| CSR | Clinical Study Report |
| CTA | computed tomography angiography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| ESR | erythrocyte sedimentation rate |
| FDA | Food and Drug Administration |
| 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 |
| IV | Intra Venous |
| LDH | lactate dehydrogenase |
| MRA | magnetic resonance angiography |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| PD | pharmacodynamic |
| PET-CT | positron emission tomography- computed tomography |

| Abbreviation | Definition |
|---|---|
| pH | negative logarithm of hydrogen ion concentration (pondus hydrogenii) |
| PK | pharmacokinetic |
| PMR | polymyalgia rheumatica |
| Q4W | every 4 weeks |
| RA | rheumatoid arthritis |
| RBC | Red Blood Cell |
| SC | subcutaneous |
| sIL-6R | soluble interleukin-6 receptor |
| sJIA | systemic juvenile idiopathic arthritis |
| TB | Tuberculosis |
| TCZ | Tocilizumab |
| ULN | upper limit of normal |
| WBC | White Blood Cell |

## 1. BACKGROUND

Tocilizumab (TCZ) has been evaluated in two completed randomized controlled trials in patients with Giant Cell Arteritis (GCA). In the Phase III WA28119 (GiACTA) study, 149 patients with GCA received subcutaneous (SC) TCZ (Stone et al. 2017), and based on the data from this trial, the SC formulation of TCZ was approved for the treatment of GCA in multiple countries worldwide. In a second study, the Phase II, investigator-initiated ML25676 study, 20 patients with GCA received intravenous (IV) TCZ (Villiger et al. 2016).

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.

The ML25676 study indicated a positive benefit-risk profile for IV TCZ (8 mg/kg IV dose every 4 weeks (Q4W) regimen) in GCA similar to that observed for the approved SC route. However, PK data from the study are sparse, and although observed trough exposures were within the therapeutic range established in study WA28119, model based predictions showed that average exposures (but not peak concentrations) over a dosing interval at steady state are higher than those observed in the RA population at the same dose. Therefore, in order to supplement the pharmacokinetic (PK) data collected in ML25676 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 WP41152 will examine exposures achieved at steady state from multiple doses of 6 and 7 mg/kg IV TCZ Q4W.

This document describes the statistical methods for the analysis of the efficacy, pharmacokinetics, pharmacodynamics, and safety of 6 and 7 mg/kg of TCZ administered by IV infusion Q4W to patients with GCA.

## 2. STUDY DESIGN

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.

## 2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Study Schema in Appendix 2.

## 2.2 ENDPOINTS

All assessments and procedures are listed with the relevant schedule detailed in the Schedule of Activities Table in Appendix 3. Additional information about the Schedule of Pharmacokinetic, IL-6, and sIL-6R Samples are provided in Appendix 4.

### 2.2.1 Pharmacokinetic 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

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.

### 2.2.2 Pharmacodynamic 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

### 2.2.3 Safety Endpoints

- Nature, frequency, severity, and causality of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).
- Clinical safety laboratory results collected at specified timepoints.
    - Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
    - 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
    - Lipid panel includes total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides

- 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)
- Viral serology includes HBsAg, total hepatitis B core antibody, and hepatitis C virus antibody

- Vital signs: pulse rate, systolic and diastolic blood pressure, temperature collected at specified timepoints. Blood pressure measurements should be obtained prior to the infusion.
- Immunogenicity assessment (anti-drug antibodies) for patients withdrawing from the study because of serious or non-serious hypersensitivity reaction.

### 2.2.4 Exploratory Efficacy 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

## 2.3 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 was followed for sample size. 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.

### 2.4 ANALYSIS TIMING

There will be final analysis and Clinical Study Report (CSR) when all patients have reached the end of the study: the end of this study is defined as the date when the last patient, last visit of Period 2 occurs, which corresponds to approximately 28 days after the last dose of Period 2.

## 3. STUDY CONDUCT

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. If the dropout rate before Period 2 and/or variability are higher than planned, additional patients may be directly enrolled in Period 2. Data from all patients receiving 6 mg/kg TCZ IV Q4W in Period 2 will be combined.

Although five doses (Q4W) at each dose level are sufficient to achieve the primary study objectives, if 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.

### 3.1 RANDOMIZATION

The study is not randomized.

## 4. STATISTICAL METHODS

Data collected during the 2 periods of treatment will be analyzed separately in general. Summaries of Period 2 will include patients that have completed Period 1 and may also include patients that have entered Period 2 directly.

### 4.1 ANALYSIS POPULATIONS

Disposition summaries will be based on the All Patients population. Medical history data, including surgery and procedures and baseline conditions, will be summarized descriptively using the safety population. Analysis of safety and pharmacodynamic data will be based on the safety population and presented by period group.

#### 4.1.1 All Patients Population

The All Patients population will include all subjects enrolled in the study within any study period, i.e. all patients present in the clinical database .

### 4.1.2 Efficacy Population

The Efficacy population will consist of all patients who received at least one dose of study drug and had at least one efficacy assessment in any study period.

### 4.1.3 Pharmacokinetic-Evaluable Population

The Pharmacokinetic (PK) analysis population will consist of patients who have received at least one dose of TCZ and have at least one valid PK sample in a given study period.

### 4.1.4 Pharmacodynamic Population

The Pharmacodynamic (PD) analysis population will consist of patients belonging to Safety analysis population.

### 4.1.5 Safety Population

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 in any study period.

## 4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who enroll, discontinue, or complete each study period and the study overall will be summarized for the All Patient population. Reasons for premature study drug discontinuation will be listed. Major protocol deviations will be listed by site and evaluated for their potential effects on the interpretation of study results. A summary of all enrolled patients will be provided by country and investigator. In addition, a listing of protocol deviations related to epidemic/pandemic will be provided in order to document any potential impact of the COVID-19 pandemic on the study.

## 4.3 SUMMARIES OF BASELINE DATA

For baseline summaries of Period 2, for data that are only collected once at the start of the study, the original baseline data from Period 1 will be used for Patients entering Period 2 after completion of Period 1.

### 4.3.1 Demographics and Disease Characteristics

Demographic and baseline characteristics will be summarized using mean, standard deviation, median, minimum, and maximum for continuous variables and proportions for categorical variables, as appropriate for the Safety population. Demographic and baseline characteristics will be listed.

Demographic and baseline disease characteristics will be summarized for period 1 (separately by dose period only if any subject will be recruited directly into period 2) as described in the following sections.

**Demographics**

- Sex
- Age
- Height
- Weight
- Race
- Ethnicity
- Smoking history

**Disease Characteristics**

- Patient in Clinical Remission at period day 1
- Erythrocyte sedimentation rate (ESR) at period day 1
- C-reactive protein (CPR) at period day 1
- Duration of Disease (GCA) at period Day 1
- Steroid use with GCA indication at period Day 1 (to be derived from concomitant medication use for GCA)
- GCA characteristics at diagnosis
    - Age ≥ 50 years
    - History of ESR ≥ 50 mm/h
    - History of CRP ≥ 2.45 mg/dL
    - Localized headache
    - Scalp tenderness
    - Temporal artery tenderness
    - Temporal artery decreased pulsation
    - Ischemia-related vision loss
    - Otherwise unexplained mouth or jaw pain upon mastication
    - Symptoms of PMR
    - Positive Temporal Artery Biopsy (TAB)
    - Large vessel vasculitis
- Was Temporal Artery Biopsy (TAB) performed?
- Was angiography or cross-sectional imaging study performed? If yes, which imaging study was performed (MRA, MRI, CTA, PET-CT, OTHER).

In addition, any positive tuberculosis screening, abnormal ECG or chest X-ray results at screening will be listed using the safety population.

### 4.3.2 Medical history

Medical history and baseline conditions will be summarized for period 1 (separately by dose period only if any subjects are recruited directly into period 2) using the Safety population. A glossary showing the mapping of investigator verbatim terms to diseases will be produced for the medical history data.

## 4.4 SURGERIES AND PROCEDURES

A listing of any previous or ongoing surgeries and procedures will be produced using Safety population.

## 4.5 PREVIOUS AND CONCOMITANT MEDICATIONS

Descriptive summaries of any previous treatment(s) will be produced. Previous medication consists of any treatments that stop prior to initiation of study drug.

Concomitant medications will be summarized separately by indication (for GCA and not for GCA). When summarizing concomitant medications, medications taken during the two dose periods will be summarized together.

A glossary showing the mapping of investigator verbatim terms to medication coded terms will be produced for previous or concomitant medication. All Analyses will be presented using Safety population.

## 4.6 VISIT WINDOWS

Endpoints collected according to scheduled visits will be assigned to a study week using the actual study day of the assessment; data collected at withdrawal visits and any unscheduled visits will also be mapped to the scheduled time points. Time windows will be continuous from the midpoint between two consecutive study visits to the next midpoint, and will be dependent on the schedule of assessments for each variable independently. An example table of time windowing for the exploratory endpoints is shown below (Table 1) for dose Period 1. Mapping of other variables will similarly be based on the scheduled visits. Data will never be mapped to visits for which the assessment was not scheduled in the protocol.

**Table 1 Time Windows for Assigning Assessment Study Days to Study Visits (Weeks) for Efficacy Exploratory Endpoints, CRP, ESR**

| Study visit within period (1 or 2) | Scheduled study day ± 3 days | Efficacy time window[a] |
|---|---|---|
| Baseline | 1 | ≤ 2 |
| Week 4 | 29 | > 2 to ≤ 43 |
| Week 8 | 57 | > 43 to ≤ 71 |
| Week 12 | 85 | > 71 to ≤ 99 |
| Week 16 | 113 | > 99 to ≤ 116 |
| Week 17 | 120 | > 116 to ≤ 123 |
| Week 18 | 127 | > 123 to ≤ 130 |
| Week 19 | 134 | > 130 to ≤ 137 |
| Week 20 [b] | 141 | > 137 to ≤ 144 or day of first 6mg/kg dose |
| For patients with a sixth dose | | |
| Week 16 | 113 | > 99 to ≤ 127 |
| Week 20 | 141 | > 127 to ≤ 144 |
| Week 21 | 148 | > 144 to ≤ 151 |
| Week 22 | 155 | > 151 to ≤ 158 |
| Week 23 | 162 | > 158 to ≤ 165 |
| Week 24 [b] | 169 | > 165 to ≤ 172 or day of first 6mg/kg dose |

[a] Use value nearest to scheduled study day.

[b] Assessments on day of first 6 mg/kg dose will also considered as the last assessment of period 1.

A similar scheme should be adopted for dose Period 2, restarting computation of number of weeks and days from baseline (first 6 mg/kg dose) of Period 2.

If more than one particular efficacy assessment occurs within the same time window, then the nearest non-missing assessment to the nominal timepoint will be assigned to that visit. If there are two (or more) efficacy assessments that occur the same time away from the nominal timepoint, then the latest assessment will be assigned to that visit. Similar approach will be applied for PD assessments.

If more than one particular safety assessment (e.g., laboratory result or vital sign) occurs within the same time window then the worst value will be assigned to the visit. The last value from screening will be used for baseline assessments of safety if there is no baseline (study day 1) value.

For summaries of data not collected by visit, such as AEs, medical history, and concomitant medications, all data up will be included.

## 4.7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

### 4.7.1 Pharmacokinetic Analyses

The PK analysis will be conducted by the Sponsor's department of clinical pharmacology and outputs will be produced by an external vendor.

The PK analysis population will consist of patients who have received at least 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.

### 4.7.2 Pharmacodynamic Analyses

The PD analyses will use the safety analysis population.

Serum concentration data will be summarized and plotted by visit and dose level (i.e. study period), with dose levels in separated tables/plots. All individual patient data will be plotted by week of assessment and dose level will be labeled with a different color. Absolute and change from baseline for CRP and ESR results will be summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum) by visit and dose level. Separate summary tables for serum concentration of IL-6 and sIL-6R (mean, standard deviation, median, minimum, and maximum) will be produced by visit and dose level for absolute values and change from baseline. Summary statistics will also be presented by day of intensive sampling after the last dose of the study period (i.e. by steady state day: Day 1, 8, 15, 22 and 29 for CRP and ESR, Day 1 and Day 29 for IL-6 and sIL-6R). Note that intensive sampling can occur after the fifth or sixth dose within each dosing period, according to the investigator decision.

Summary plots will be provided visit and dose level: CRP and ESR absolute value data will be plotted as median and interquartile ranges while IL-6 and sIL-6R will be plotted as mean and sample error of the mean. Summary plots will also be provided by steady state day and dose level.

A listing of PD data will be reported, with specification of dose period, visit, dose amount.

## 4.8 EXPLORATORY EFFICACY ANALYSIS

The exploratory efficacy analyses will be performed using the efficacy population.

The proportion of subjects with flare (as collected in the CRF) will be computed at each visit separately for each dose period. The proportion of subjects in remission (defined as absence of flare and normalization of CRP, i.e. <1mg/dL at lab examination) will also be

computed at each visit separately for each dose period. Proportions will use the number of patients with valid data as the denominator for computation at each visit, as no imputation rule will be used for missing values.

A listing of signs and symptoms, ESR, and CRP, at the time of flare will be produced for patients with flare, by dose period. A listing of signs and symptoms, ESR, and CRP, by visit, will also be produced for all patients, by dose period.

### 4.8.1 Sensitivity Analyses

No sensitivity analyses are planned for this study.

### 4.8.2 Subgroup Analyses

No subgroup analyses are planned for this study.

## 4.9 SAFETY ANALYSES

The safety analysis will be performed on the safety population. Any safety analyses will be presented separately for each dose period.

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

Values, along with change from baseline, will be summarized by visit and dose period 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 dictionary.

### 4.9.1 Exposure of Study Medication

The number of doses received will be summarized for each dose period. A listing of patients in each period detailing dosing of TCZ will be prepared.

Compliance will be summarized by the number of patients with missed infusion.

### 4.9.2 Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) will be used as the thesaurus for AEs and disease codes, and the INN (International Non-Propriety Name) dictionary will be used for treatments. A glossary of these codes will be produced. Generally AEs will be classified and presented separately according to the dose period of onset.

Only treatment-emergent AEs will be summarized. Treatment-emergent events are defined as those AEs with observed or imputed onset date on or after the start date of trial treatment. Only where the most extreme intensity is greater than the initial intensity (or if most extreme intensity is not missing and initial intensity is missing) will events

with an onset date prior to the start of trial treatment be considered treatment-emergent. An AE with a completely missing start date will be assumed to be treatment-emergent unless the AE has a complete non-imputed end date that is prior to study Day 1. Adverse events will be coded and tabulated by system organ class (SOC) and/or preferred term. In tabulations, preferred terms and their associated SOC will be presented in order of descending frequency summed across the dose periods. Adverse events will also be tabulated by severity and relationship to study medication as indicated by the investigator.

Adverse event rates per 100 patient-years exposure (defined as the number of events/total duration in the study multiplied by 100) will be calculated for each AE preferred term and SOC, along with the corresponding 95% CIs for the rates of the SOC (exact based on the $\chi^2$ distribution [Ulm et al. 1990]).

The following will also be summarized:

- Serious adverse events
- Adverse events leading to withdrawal from treatment
- Adverse Events leading to withdrawal from study
- Adverse events leading to death

Adverse events of special interest will be defined using published Standard MedDRA Queries (SMQs) or AE Grouped Terms (AEGTs) defined by Roche Drug Safety. The groupings of AEs will include but may not be limited to the following:

- Serious Infections (Infections and Infestations SOC filtered for serious)
- Opportunistic Infections (Roche Standard AEGT Opportunistic Infections)
- Hypersensitivity Reactions (AEs during or within 24 hours of TCZ treatment and not unrelated to study medication)
- Clinically Significant Hypersensitivity Reactions (AEs during or within 24 hours of TCZ treatment, not unrelated to study medication and leading to study treatment discontinuation)
- Anaphylactic reactions according to Sampson's criteria (Roche Standard AEGT Basket according to Sampson’s criteria (Sampson et al. 2006)
- Anaphylactic Reaction (SMQ narrow)
- Serious Hepatic Events (Hepatic Failure, Fibrosis and Cirrhosis and Other Liver Damage-Related Conditions (SMQ wide + Hepatitis, Non-Infectious SMQ wide)
- Gastrointestinal Perforations (Gastrointestinal Perforation SMQ wide)
- Demyelinating Disorders (Demyelination SMQ narrow)
- Myocardial infarction (MI)/acute coronary syndrome (MI SMQ narrow)
- Stroke (Haemorrhagic Central Nervous System Vascular Conditions SMQ narrow + Ischaemic Central Nervous System Vascular Conditions SMQ narrow)
- Serious Bleeding (Haemorrhage Terms [Excluding Lab Terms] SMQ wide filtered for serious)

- Malignancies (Malignant Tumors SMQ narrow + Tumors of Unspecified Malignancy SMQ narrow)
- Suspected transmission of an infectious agent by the study drug (STIAMP), 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.
  The two MedDRA preferred terms to capture STIAMP AEs will be “Suspected transmission of an infectious agent via product” and “Transmission of an infectious agent via product”

Selected AEs (AEs selected for analysis but not part of protocol-defined expedited reporting requirements):

- Infection (Infections and Infestations SOC)
- Neutropenia (Roche standard AEGT for neutropenia)
- Thrombocytopenia (thrombocytopenia SMQ wide)

A glossary showing the mapping of investigator verbatim terms to preferred terms will be produced for all AEs included in the analysis. For each AE of special interest table based on SMQs/AEGTs, a corresponding listing of the preferred terms that comprise the SMQ will be produced.
A listing of for the following will be produced:

- Deaths
- Adverse events leading to dose modification or interruption
- Adverse events leading to drug withdrawn
- Adverse events leading to study discontinuation
- Adverse events
- Serious adverse events
- Serious adverse events caused by a protocol-mandated intervention prior to initiation of study drug, all screened patients
- AESIs (listed above)
- Selected AEs (listed above)

Pregnancy data will be listed. Pregnancies will be identified using the urine test results.

### 4.9.3 Laboratory Data

All laboratory data will be converted to SI units. The International Standard for the Handling and Reporting of Laboratory Test Data (Data Analysis Guidance) will be used to implement reference ranges and marked abnormalities for laboratory data where

possible. Summary tables will detail the actual values and changes from baseline of the laboratory parameters over visits by period.

Summaries of the number of patients by highest CTC grade post-baseline for hematology, chemistry, hepatic lab parameters (liver enzymes, alkaline phosphatase and total bilirubin) and lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) will be produced (for summaries referring to NCI CTCAE grading).

For neutrophils, platelets, hepatic lab parameters and lipids, the number of patients will be summarized by category for baseline and worst post baseline result.

For neutrophils, a categorical analysis of the pattern of elevations Grade 3 or higher will be produced (i.e. % patients with no depression, depressions at a single timepoint, consecutive depressions, consecutive depressions sustained, non-consecutive depressions).

For lipids, a categorical analysis of the pattern of elevations in total cholesterol (>=240 mg/dL) and a categorical analysis of the pattern of elevations in LDL (>=160 mg/dL) will be produced (i.e. % patients with no elevation, elevation at a single timepoint, consecutive elevations, consecutive elevations sustained, non-consecutive elevations).

Similar categorical analysis of the pattern of elevations will be produced liver enzymes and total bilirubin.

Listing will be produced for patients who had simultaneous elevations ≥3 x ULN in ALT or AST and ≥2 x ULN in total bilirubin (laboratory criteria for Hy's Law).

Patients with marked abnormalities will be listed.

Any analysis will be performed separately by dose period.

**Lipid Data**

Fasting lipids consist of total cholesterol, triglycerides, HDL, and LDL, and these will be summarized separately from the other laboratory parameters when referencing gradings or shifts.

Threshold for the presentation of lipid data are defined by the National Cholesterol Education Program Adult Treatment Panel III (2001) and are shown in Table 2.

**Table 2 National Cholesterol Education Program (ATPIII) Thresholds**

| | | | | | |
|---|---|---|---|---|---|
| **LDL** (mg/dL) | <100 (optimal) | 100–129 (normal) | 130–159 (borderline high) | ≥160 (high) | |
| **HDL** (mg/dL) | <40 (low) | 40–59 (normal) | | ≥60 (high) | |
| **Total cholesterol** (mg/dL) | <200 (desirable) | | 200–239 (borderline high) | ≥240 (high) | |
| **Triglycerides** (mg/dL) | <150 (normal) | | | 150–499 (high) | ≥500 (very high) |

ATPIII = Adult Treatment Panel III.

### 4.9.4 Vital Signs

Summary tables will detail the actual values and changes from baseline of the laboratory parameters over visits and by dose period for pulse rate, systolic blood pressure, diastolic blood pressure, body temperature, body weight and body mass index.

Blood pressure will also be summarized by visit using the following JNC 7 (Joint National Committee) categories reported in Table 3.

**Table 3 Blood Pressure JNC 7 Category Criteria**

| Blood Pressure Category | Criteria |
|---|---|
| Normal | SBP < 120 mmHg and DBP < 80 mm Hg |
| Pre-hypertension | 120 ≤ SBP < 140 mmHg or 80 ≤ DBP < 90 mmHg |
| Stage I hypertension | 140 ≤ SBP < 160 mmHg or 90 ≤ DBP < 100 mmHg |
| Stage II hypertension | SBP ≥ 160 mmHg or DBP ≥ 100 mmHg |

DBP = diastolic blood pressure; JNC = Joint National Committee; SBP = systolic blood pressure.

### 4.9.5 Immunogenicity Assessment

Blood samples for the presence of anti-TCZ antibodies should be obtained for all patients at baseline and for any patients withdrawing from the study because of serious or non-serious hypersensitivity reaction, including anaphylaxis, at the time of occurrence of the event and approximately 8 weeks after the last dose.

All samples will be tested by screening assay, and those samples that are positive will be further analyzed by a confirmation assay to confirm antibodies' specificity. If the confirmation assay is positive, two additional tests will be performed: a neutralizing assay to measure the antibodies' neutralizing potential and an IgE assay to confirm if the anti-TCZ antibodies are of IgE isotype.

Given the testing strategy, for the purpose of the summary tables, if the results of the confirmation or neutralizing assays are missing for a sample, then they will be assumed negative if the screening assay is negative. If the screening assay is positive and the

confirmation assay is negative, then the neutralizing assay will be assumed negative if missing.

A listing of all patients who have a positive immunogenicity assay result at any timepoint will be produced for safety population flagging the dose period.

## 4.10 MISSING DATA

Partial dates for concomitant medications, exposure and AEs (AE start date) will be imputed.

## 4.11 INTERIM ANALYSES

No efficacy interim analysis is planned.

PK data will be analyzed on an ongoing basis, but interim results will not be included in the final clinical study report; only the final analysis will be included.

An evaluation of the data at the end of Period 1 will be undertaken. If the dropout rate and/or variability are higher than expected, 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.

# 5. REFERENCES


Common Terminology Criteria, Version 5.0, National Cancer Institute, USA, Published November 27, 2015.

Data Analysis Guidance: International Standard for the Handling and Reporting of Laboratory Test Data, Roche Global Data Standards Repository, version 1.1, 19 APR 2018.

Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. 2001. Available from https://www.fda.gov/downloads/drugs/guidances/ucm070244.pdf.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.

Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med 2017;377 ;317–28.

Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990;131:373−5.

Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:1921–7.

Wang Y, Jadhav PR, Lala M, et al. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J. Clin Pharmacol 2012;52:1601–6.

# Appendix 1 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** |
| **PROTOCOL NUMBER:** | WP41152 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2018-004718-17 |
| **IND NUMBER:** | 113,654 |
| **TEST PRODUCT:** | Tocilizumab (RO4877533) |
| **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 leves 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 may be directly enrolled in 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 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 per the 1990 American College of Rheumatology criteria fulfilled at the time of diagnosis

- For patients entering Period 1, patients must be receiving treatment with TCZ 8 mg/kg IV Q4W and received at least five consecutive doses prior to baseline and be in remission at baseline
- For patients entering Period 2, prior to the first dose of 6 mg/kg TCZ IV, patients must be in remission at the end of Period 1
- 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 remain abstinent (refrain from heterosexual intercourse) or 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 remain abstinent or 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.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

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.

  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 $\mu$mol/L) in female patients and $>$ 1.6 mg/dL (141 $\mu$mol/L) in male patients
- ALT or AST $>$ 1.5 $\times$ upper limit of normal (ULN)
- Total bilirubin $>$ ULN
- Platelet count $<$ 100 x$10^9$/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 $<$ 2.0 $\times$ $10^9$/L (2000/$mm^3$)
- 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

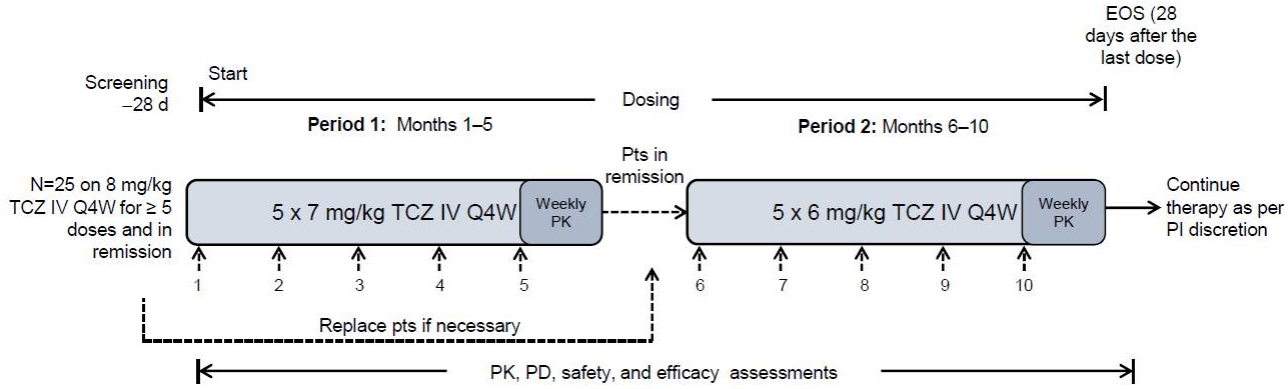
In order to provide a precise characterization of PK parameters ($C_{trough}$, $C_{max}$, and $AUC_{4weeks}$), in this study, a hybrid of two approaches will be followed. The first of these approaches is the guidance for estimation of sample size in pediatric studies, which requires a study to be prospectively 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.

# Appendix 2 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.

# Appendix 3 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 | | | | | x | | | x | | | | | x | x |
| Viral serology [k] | x | | | | | | | | | | | | | | | | | | |
| Lipid panel [l] | | x | | | | | | | | x | | | | | | | | x | x |

# Appendix 3 Schedule of Activities (cont.)

| 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 |
| Pregnancy test [m] | x | | | | | | | | | | | | | | | | | x | x |
| Urinalysis [n] | 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 4 | | | | | | | | | | | | | | | | | x [o] |
| TCZ PK | | See Appendix 4 | | | | | | | | | | | | | | | | | x [o] |
| Anti-TCZ Ab | | x | | | | | | | | | | | | | | | | | x [o] |
| Adverse events [p] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant medications [q] | 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 3 Schedule of Activities (cont.)

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

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

[m] 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.

[n] 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).

# Appendix 3 Schedule of Activities (cont.)

[o] 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.

[p] 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.

[q] 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 4 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.