# STATISTICAL ANALYSIS PLAN

**Study: RA0138**

**Product: Certolizumab Pegol**

# A MULTI-CENTER, OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS OF CERTOLIZUMAB PEGOL IN ADULTS WITH ACTIVE RHEUMATOID ARTHRITIS USING AN ELECTROCHEMILUMINESCENT IMMUNO-ASSAY

## SHORT TITLE:

A study to evaluate the PK of certolizumab pegol in adults with active rheumatoid arthritis using an electrochemiluminescent immune-assay (ECLIA).

Sponsor Name: UCB Biopharma SRL

Legal Registered Address: Allée de la Recherche 60 1070 Brussels BELGIUM

Regulatory Agency Identifier Number(s):

| Registry | ID |
|---|---|
| IND Number: | 009869 |
| | |
| | |

# TABLE OF CONTENTS

LIST OF ABBREVIATIONS ..... 6
1 INTRODUCTION ..... 7
1.1 Objectives and Estimands/Endpoints ..... 9
1.2 Study design ..... 9
1.2.1 Overall Design ..... 9
1.2.2 Number of Participants ..... 10
1.2.3 Treatment Groups and Duration ..... 10
1.2.4 Schema- Schedule of Activities ..... 11
2 STATISTICAL HYPOTHESES ..... 12
3 SAMPLE SIZE DETERMINATION ..... 12
4 POPULATIONS FOR ANALYSIS ..... 12
5 STATISTICAL ANALYSES ..... 12
5.1 General Considerations ..... 12
5.1.1 General study level definitions ..... 13
5.1.1.1 Analysis Time Points ..... 13
5.1.1.2 Protocol Deviations ..... 15
5.1.1.3 Treatment assignment and treatment groups ..... 15
5.1.1.4 Center pooling strategy ..... 15
5.1.1.5 Coding dictionaries ..... 15
5.1.1.6 Multicenter studies ..... 16
5.2 Participant Dispositions ..... 16
5.3 Primary Endpoint(s) Analysis ..... 17
5.3.1 Definition of endpoint(s) ..... 17
5.3.2 Main analytical approach ..... 17
5.3.2.1 Handling of dropouts or missing data ..... 18
5.3.3 Sensitivity analysis ..... 18
5.3.4 Supplementary analyses ..... 18
5.4 Secondary Endpoint(s) Analysis ..... 18
5.4.1 Key secondary endpoint(s) ..... 18
5.4.1.1 Definition of endpoint(s) ..... 18
5.4.1.2 Main analytical approach ..... 18
5.4.1.3 Sensitivity analysis ..... 20
5.4.1.4 Supplementary analyses ..... 20
5.4.2 Supportive secondary endpoint(s) ..... 20
5.5 Tertiary/Exploratory Endpoint(s) Analysis ..... 20
5.5.1.1 Immunological Analyses ..... 21
5.5.1.2 RAPID3 analysis ..... 25

5.5.1.3 Adverse Events ..... 25
5.5.1.4 Vital Signs ..... 26
5.5.1.5 Clinical laboratory evaluations ..... 27
5.6 (Other) Safety Analyses ..... 29
5.6.1 Extent of Exposure ..... 29
5.6.1.1 Electrocardiograms ..... 29
5.6.1.2 Electrocardiogram Values Over Time ..... 29
5.6.2 Additional Safety Assessments ..... 30
5.6.2.1 Other safety endpoint(s) ..... 30
5.7 Other Analyses ..... 30
5.7.1 Other endpoints and/or parameters ..... 30
5.7.1.1 Pharmacokinetics ..... 30
5.7.1.2 Pharmacodynamics ..... 30
5.7.1.3 Genomics ..... 30
5.7.1.4 Tuberculosis screening (IGRA) and Tuberculosis Questionnaire ..... 30
5.7.1.5 COVID-19 Impact ..... 30
5.8 Subgroup analyses ..... 31
5.9 Interim Analyses ..... 31
5.10 Data Monitoring Committee (DMC) or Other Review Board ..... 31
6 SUPPORTING DOCUMENTATION ..... 31
6.1 Appendix 1 Non-key analysis specifications ..... 31
6.1.1 Baseline characteristics and demographics ..... 31
6.1.2 Protocol deviations ..... 32
6.1.3 Medical history ..... 33
6.1.4 History of Rheumatoid Arthritis ..... 33
6.1.5 Prior/concomitant medications ..... 34
6.1.5.1 Prior medication definition ..... 34
6.1.5.2 Concomitant medication definition ..... 34
6.1.6 Data derivation rules ..... 34
6.1.6.1 Handling of repeated and unscheduled measurements ..... 34
6.1.6.2 Handling of Dates and times ..... 35
6.1.7 AEs of Special Interest (AESIs) ..... 37
6.1.8 Potentially Clinically Significant Criteria for Safety Endpoints ..... 40
6.1.9 Compliance ..... 40
6.2 Appendix 2: Changes to Protocol-Planned Analyses ..... 40
7 REFERENCES ..... 40
8 APPENDICES ..... 42
8.1 RAPID3 Assessment ..... 42

8.2 SAP Amendment 1 ..... 43

# VERSION HISTORY

This Statistical Analysis Plan (SAP) for study RA0138 is based on the protocol amendment 2 dated 18 Mar 2021.

| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| 1.0 | 23-APR-2021 | Not Applicable | Original version |
| 2.0 | 30-Aug-2022 | Section 5.1.1.2 Anti-drug antibodies analysis has been added new analysis | To be consistent with CZP ISAP |

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADAb | Antidrug Antibody |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ALQ | Above The Limit Of Quantification |
| AST | Aspartate Aminotransferase |
| ASP | All Subject Population |
| $AUC_{0\text{-}tau}$ | Area Under The Plasma Concentration-Time Curve From Time Zero To Infinity. |
| BLQ | Below The Limit Of Quantification |
| BMI | Body Mass Index |
| CRF | Case Report Form |
| CI | Confidence Interval |
| $C_{min}$ | Minimum Observed Plasma Drug Concentration |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CV | Coefficient Of Variation |
| CZP | Certolizumab Pegol |
| DCP | Data Cleaning Plan |
| DEM | Data Evaluation Meeting |
| DILI | Drug Induce Liver Injury |
| ECG | Electrocardiogram |
| ECLIA | Electrochemiluminescent Immuno-Assay |
| EMA | European Medicines Agency |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FDA | Food and Drug Administration |
| geoCV | Geometric Coefficient Of Variation |
| geoMean | Geometric Mean |
| ICF | Informed Consent Form |
| ICH | International Council For Harmonisation |
| IGRA | Interferon-Gamma Release Assay |
| IMP | Investigational Medicinal Product |
| IPD | Important Protocol Deviation |
| LLOQ | Lower Limit Of Quantification |
| MDHAQ | Multi-dimensional Health Assessment Questionnaire |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTX | Methotrexate |

| | |
|---|---|
| NI | Negative Immunodepletion |
| NS | Negative Screen |
| pJIA | Polyarticular Juvenile Idiopathic Arthritis |
| PI | Positive Immunodepletion |
| PK | Pharmacokinetic |
| PKS | Pharmacokinetic Set |
| PS | Positive Screen |
| PT | Preferred Term |
| Q2W | Every 2 Weeks |
| RA | Rheumatoid Arthritis |
| RAPID3 | Routine Assessment of Patient Index Data 3 |
| RCTC | rheumatology common toxicity criteria |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| sc | Subcutaneous |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SFU | Safety Follow-up |
| SS | Safety Set |
| TB | Tuberculosis |
| TFL | tables, figures and listings |
| TEAE | treatment-emergent adverse event |
| ULN | Upper Limit Of Normal |
| US | United States |
| WHODD | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of RA0138. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity, with the following study documents:

1. Final Protocol Amendment 2: 18 Mar 2021

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP but they will be described in a separate statistical analysis plan. However, if analysis definitions have to be modified or updated, a SAP amendment will be required. The content of this SAP is compatible with:

- The International Council for Harmonisation (ICH) and E9 guidance documents[2]

- Food and Drug Administration (FDA) guidance[3]
- European Medicines Agency (EMA) guidelines[4,5]
- Canada Health ministry guidances[6,7].

UCB is the sponsor and PAREXEL International is the Contract Research Organization (CRO) for this study.

## 1.1 Objectives and Estimands/Endpoints

**Table 1–1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the PK of CZP (utilizing the ECLIA method) in adults with active RA | • PK parameters ($C_{min}$ and $AUC_{0\text{-}tau}$) following 10 weeks of CZP dosing |
| **Secondary** | |
| • To evaluate CZP exposure over a maximum of 24 weeks administration to adults with active RA<br>• To evaluate the safety of CZP in adults with active RA | • CZP plasma concentrations over the duration of study<br>• Treatment-emergent SAEs and TEAEs leading to withdrawal from the time of the first CZP dose through the SFU Visit |
| **Other** | |
| • To assess the occurrence of anti-CZP antibodies (utilizing the ECLIA method) over the duration of the study | • ADAb screening status (positive or negative screen), confirmatory status (positive or negative immunodepletion), and the titer for "positive immunodepletion" samples at each scheduled assessment after first CZP dose through SFU |
| • To assess the efficacy of CZP | • Change in Routine Assessment of Patient Index Data 3 (RAPID3) from Baseline to Week 12 |
| • To evaluate other safety parameters | • TEAEs, vital signs, and laboratory assessments |

ADAb=antidrug antibody; AE=adverse event; CZP=certolizumab pegol; ECLIA=electrochemiluminescent immuno-assay; PK=pharmacokinetic; RA=rheumatoid arthritis; RAPID3=Routine Assessment of Patient Index Data; SAE=serious adverse event; SFU=Safety Follow-up Visit; TEAE=treatment-emergent adverse event

## 1.2 Study design

### 1.2.1 Overall Design

This is a multi-center, open-label Phase 1B study to assess the PK, safety, and tolerability of CZP in adults with active RA. In this 24-week study, study participants (ie, male or female participants 18 to 69 years of age inclusive) who are naïve to CZP and are eligible to receive a biologic for RA will receive CZP in subcutaneous (sc) loading doses at Weeks 0,

2, and 4, followed by a treatment of 200mg every 2 weeks (Q2W), with the final dose taking place at Week 24.

### 1.2.2 Number of Participants

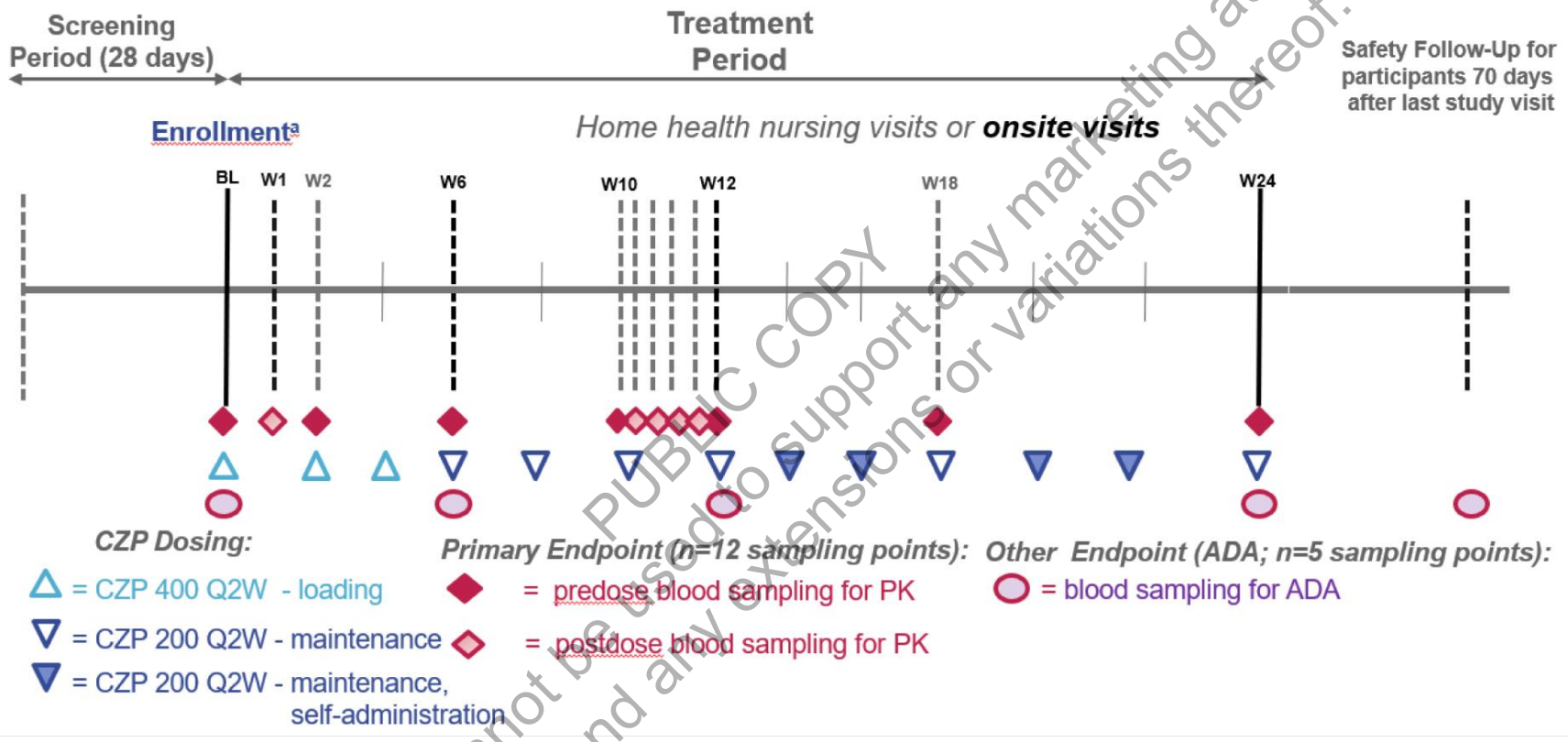
A total of 30 participants will be enrolled to receive CZP, such that a minimum of 25 evaluable participants are expected to complete Visit 13 (Week 12).

### 1.2.3 Treatment Groups and Duration

All study participants will receive CZP treatment. Study participants may be taking concomitant methotrexate (MTX); however, a minimum of 8 study participants must be enrolled who are not on concurrent administration of MTX.

The duration of the study is approximately 38 weeks. The study consists of a Screening Period (28 days), Baseline Visit, a Treatment Period (24 weeks), and a Safety Follow-up (SFU) Visit (70 days after the last study visit).

### 1.2.4 Schema- Schedule of Activities




ADAb=antidrug antibody; BL=Baseline; CZP=certolizumab pegol; PK=pharmacokinetic; Q2W=every 2 weeks; W=week
[a] CZP naïve at enrollment.

# 2 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing is planned in this study.

# 3 SAMPLE SIZE DETERMINATION

With no formal hypothesis testing, a sample size of 30 enrolled participants with 25 participants who completed Visit 13 is deemed to provide sufficient plasma CZP concentration data with the ECLIA analytical method to serve as a reference PK dataset for PK matching in the pJIA program. Further, a simulation and re-estimation method applied using a non-RA CZP population PK model indicated that a sample size of 25 participants who completed Visit 13 in a study with the PK sampling scheme as that presently planned can estimate absorption rate constant, clearance, and distribution volume with acceptable precision (relative standard deviation of <16%). Participants who withdraw from the study may be replaced at the discretion of the Investigator and Sponsor, depending on the circumstances.

# 4 POPULATIONS FOR ANALYSIS

The following analysis sets will be used in the study:

- All Study Participants (ASP) will include those study participants who are confirmed as having signed the ICF form to participate in the study.
- The Safety Set (SS) will include all study participants enrolled who receive ≥1 injection of study medication. Safety variables will be summarized using the SS.
- The Pharmacokinetic Set (PKS) is a subset of the SS, consisting of study participants who have provided plasma samples with measurable concentrations (with recorded sampling time) on at least 1 visit, and who have no important protocol deviations affecting the PK parameters.

# 5 STATISTICAL ANALYSES

## 5.1 General Considerations

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using statistical analysis system (SAS®, SAS Institute, Cary, NC, US) version 9.3 or higher using validated program code according to relevant standard operating procedures. PK parameters will be calculated by Non-Compartmental Analysis (NCA) methods from the concentration-time data with actual time using Phoenix® WinNonlin® Version 8.3 or higher following UCB guideline: Guideline on performing NCA analysis , Nov 2017.

In general, there will be no imputation of missing data unless otherwise stated.

For categorical parameters, the number and percentage of study participants in each category will be presented. The denominator for percentages will be based on the number of study participants appropriate for the purpose of the analysis. For continuous parameters, descriptive statistics will include number of study participants, arithmetic mean, standard deviation, median, minimum, and maximum (with 25th and 75th percentiles as optional).

Baseline is defined as the last nonmissing measurement collected before the first injection.

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all study participants fulfill certain criteria, the percentage value will be displayed as 100

- For values where the absolute frequency is zero, there will be no percentage displayed at all
- All other percentage displays will use 1 decimal place

Percentages displayed based on continuous data (eg, percentage changes from baseline) will be displayed to 1 decimal place.

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean (arithmetic and geometric), SD and median will use 1 decimal place more than the original data
- geoCV will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places as the original value
- If no study participants have data at a given time point, for example, then only n=0 will be presented. If n<3, then only n, minimum and maximum will be presented. If n=3, then only n, mean, median, minimum and maximum will be presented. The other descriptive statistics will be left blank.

For CZP plasma concentration, the geometric mean and corresponding coefficient of variation will be presented. The geometric coefficient of variation (CV) is calculated as sqrt (exp(std ln^2)-1)*100, where std ln is the standard deviation of the log-transformed data.

All tabulations will be performed for PKS, visit and timepoint (where applicable). Data listings containing all documented data and all derived data will be generated.

### 5.1.1 General study level definitions

#### 5.1.1.1 Analysis Time Points

##### 5.1.1.1.1 Relative day

Relative day for an event will be derived with the date of the first sc injection of study drug as reference.

Relative days for an event or measurement occurring before the date of the sc injection of study drug are calculated as follows:

Relative Day = [(Event Date – Date of First Injection)]

The relative day for an event or measurement occurring on or after the reference date to the date of the sc injection is calculated as follows:

Relative Day = [(Event Date - Date of First Injection) + 1]

In the listing, Relative Day will be presented as below: numbers with no prefix are days after first dose at visit 2 +1, '-' prefixed numbers are days before first dose at visit 2 and '+' prefixed numbers will be days after last dose at visit 15.

For PK , the relative time (hour) is calculated as the date time of each sample minus the date time of dose at the PK sample date.

#### 5.1.1.1.2 End date of the Treatment Period

*The end date of the Treatment Period will be either the date of Visit 15(Week 24) for study participants completing the Treatment Period, or the date of the Early Discontinuation Visit (EDV) for study participants who discontinued during the Treatment Period. If a participant does not have a Visit 15(Week 24)/EDV, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of study drug during the Treatment Period, whichever is later, will define the end date of the Treatment Period.*

#### 5.1.1.1.3 Study periods

The duration of the study for each study participant is approximately 38 weeks.; consisting of the following 3 periods:

- Screening Period (up to 28 days): Visit 1, Day -28 to Day -1
- Treatment Period (24 weeks) including Baseline visit: based on the first planned treatment starting from Visit 2 at Day 0 to the last planned treatment on Visit 15 at Day 168 (Week 24)
  - 400mg loading dose phase for doses at Week 0, Weeks 2 and 4 followed by 200mg Q2W maintenance dose phase thereafter (at Week 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24)
  - PK profile treatment Period: Day 72±6 hours to Day 80±6 hours. These visits may be conducted at home visit.
- Safety Follow-Up: The end of study visit will be performed on 70 days after last IMP through SFU visit.

The end of the study is defined as the date of the last visit of the last study participant in the study. Study participants are considered to have completed the study if they complete the last scheduled study visit (Screening, Baseline Visit, Treatment Period [through Week 24], and SFU). The safety follow-up visit is 70 days post last dose. If study participants are continuing onto commercial Cimzia, the safety follow-up is 30 days post last dose.

#### 5.1.1.1.4 Mapping of assessments performed at Early Discontinuation Visit

For time course displays it may be necessary to assign premature withdrawal visits to a specific study time point. In general, premature withdrawal visits should be assigned to what would have been the next scheduled visit for the particular assessment that is being summarized. This re-assignment should be based upon the study day (relative to the baseline visit date). For example, a study assesses anti-CZP antibody sampling at Baseline (Day 0), Weeks 6, 12, 24 and SFU. If a participant discontinues on day 150 of the study, and the previous assessment was done at Week 6, the next scheduled assessment would normally be Week 12. However, study Day 150 is closer to the Week 24 visit (Study Day 168). Therefore, the termination assessment should be re-assigned to the Week 24 visit. If the premature withdrawal visit of study day is tied in the middle of two visits, then earlier visit will be chosen, (assuming earlier visit also without valid datapoint also, to avoid data overwritten). For example, suppose the patient also discontinues at Day 126 ( in the midpoint of Week 24, Day 168 and Week 12, Day 84), then the Week 12, Day 84 will be assigned and firstly considered. However, if there was recently assessed at Week 12, the assessments obtained at

premature termination visit should be re-mapped and analyzed at the Week 24 visit, as there is already valid data available at the Week 12 visit.

Generally speaking, assessments at an Early Discontinuation Visit (EDV) that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. Such assessments will also be considered for Last Value.

Different domains from the same EDV may be assigned to different visit weeks. For example, the TB questionnaire is scheduled to be collected at screening, Weeks 12,and 24; RAPID3 testing at baseline, and Week 12. If a participant has screening, baseline, and an EDV, both the TB questionnaire and RAPID3 testing withdrawal assessments should map to Week 12.

#### 5.1.1.1.5 Definition of Baseline values

*Baseline is defined as the last nonmissing pretreatment measurement. Therefore, data from the Screening Visit (if available) will be used as Baseline values if data are missing at Week 0. No other data will be considered for Baseline.*

### 5.1.1.2 Protocol Deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual study participant. PK samples outside the protocol windows, missing doses or delayed doses potentially impacting PK, will be reviewed. PK sampling protocol deviations will not automatically cause their exclusion from the PKS set. The table of summary PK statistics and geometric mean PK concentration-time figure will be presented with and without those PK samples determined to be protocol deviations.

The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document at study start. Important protocol deviations will be reviewed as part of the ongoing data cleaning process.

Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this data cleaning and evaluation process, all decisions regarding important protocol deviations and exclusions from analysis populations will be made. Important protocol deviations including those that lead to exclusion from the analysis sets will be identified and documented prior to database lock.

All tabulations and listing of protocol deviations will be performed for all study participants.

### 5.1.1.3 Treatment assignment and treatment groups

This is open label and one arm study; the case of treatment misallocation will be not applicable.

### 5.1.1.4 Center pooling strategy

The data from all centers will be pooled together for analyses.

### 5.1.1.5 Coding dictionaries

All AEs and medical history will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA)® coding dictionary, using the MedDRA version 23.1. Prior and

concomitant medications will be coded for analysis using the version Sep/2020 B3 update of the World Health Organization Drug dictionary (WHO-DD). Medical procedures will not be coded.

#### 5.1.1.6 Multicenter studies

The data from all centers will be pooled together for analyses. Individual center results will not be displayed.

## 5.2 Participant Dispositions

The following summary outputs will be presented.

- **Reasons for screen failures** will be summarized using the All Study Participants (ASP), including rescreened study participants.
- **Disposition of study participants screened** will be summarized using the ASP for overall and by site. In this summary, the site number, principal investigator name, first participant in date, last participant out date, number of study participants screened will be captured by each analysis set (SS).
- **Disposition and Discontinuation Reasons** using the SS will contain the number and percentage of study participants by loading dose phase and maintenance phase.
- **Discontinuation due to AEs** will be summarized for following type of AEs using the SS:
    - AE, serious fatal,
    - AE, non-fatal,
    - Other (AE, non-serious fatal).
- **Impact of COVID-19** using the ASP will summarize number and percentage of participants in each impact category by visit.

The number of study participants who started into the study and study participants who completed or prematurely discontinued the study, as well as the reason for discontinuation, will be presented by CZP loading dose(400 mg) and CZP maintenance dose (200 mg) for SS. A participant who completed the whole study is defined as a participant who completed the last scheduled Safety-Follow-Up Visit, ie, the participant will be regarded as a completer if the safety-follow-up (Visit 16, 70 days after last IMP through SFU visit) visit was completed. The number and percentage of study participants who discontinued due to AEs will be separately summarized based on the SS.

Screen failure reasons will be summarized based on All Study Participants (ASP). A listing of study participants who did not meet study eligibility criteria (including glossary) will also be presented based on All Study Participants (ASP).

In addition, the following listings will be presented for all study participants :

- Study participant disposition (ASP)
- Study discontinuation (ASP)
- Visit dates (ASP)
- Subject analysis sets (ASP )

Study participant disposition will be listed for all study participants based on the All Study Participants (ASP), and will include the date of informed consent, date and time of dosing, date of premature termination and primary reason (if applicable), and date of final contact.

## 5.3 Primary Endpoint(s) Analysis

The primary endpoint analysis is to evaluate the PK of CZP (utilizing the ECLIA method) in adults with active RA.

Pharmacokinetics will be assessed using the PKS.

### 5.3.1 Definition of endpoint(s)

The primary PK variables will include the following PK parameters ($C_{min}$ and $AUC_{0\text{-}tau}$ ) following 10 weeks of CZP dosing.

- $AUC_{0\text{-}tau}$ : area under the curve over a dosing interval
- Cmin: Minimum plasma drug concentration during a dosage interval.

### 5.3.2 Main analytical approach

The primary PK parameters in plasma are: $C_{min}$ and $AUC_{0\text{-}tau}$.

The primary PK parameters of CZP will be summarized by MTX use at screening using descriptive statistics (number of available observations (n), arithmetic mean, median, SD, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean (assuming lognormally distributed data)). Values below the LLOQ will be reported with a clear sign indicating that they were below the LLOQ.

For calculation of the PK data (including parameter), the actual blood sampling times will be used.

All PK data will be listed and summarized for all study participants for the PKS including n, arithmetic mean, median, SD, minimum, maximum, geometric mean, geoCV and 95% CI for the geometric mean.

The following rules will apply for the PK data summaries:

- PK parameters are reported with 3 significant digits and Descriptive statistics reported to 4 significant figures for the mean, median and standard deviation (SD) and to 3 significant figures for all others.
- Values below the LLOQ will be reported as BLQ for individual data and will be substituted with LLOQ/2 for the descriptive statistics
- Descriptive statistics of PK concentrations will be calculated only if at least ⅔ of the individual data at a specific sampling timepoint are measured and are quantifiable (ie, above LLOQ) and if n≥4. If n<3, then only n, minimum and maximum will be presented and if n=3, then only n, median, minimum and maximum will be presented and the other descriptive statistics will be left blank.
- Descriptive statistics of PK parameters will be calculated only if at least ⅔ of the individual data are calculable and if n≥4. If n<3, then only n, minimum and maximum will be presented and if n=3, then only n, median, minimum and maximum will be presented and the other descriptive statistics will be left blank.

- If no study participants have data, only n=0 will be presented.
- The 95% lower and upper CI should be left blank if the SD (or equivalently the geoCV) is equal to 0
- The geoCV will be calculated using the following formula where SD is the standard deviation of the log-transformed values: geoCV (%) = sqrt[(exp(SD^2) – 1)] x 100

#### 5.3.2.1 Handling of dropouts or missing data

Measurements that are BLQ will be imputed with half of the LLOQ for the purpose of calculating the geoMean and its 95% CI, the geoCV, the arithmetic mean, and SD for summaries and figures. If any summary value (geoMean, arithmetic mean, lower CI level or minimum) is lower than LLOQ, then 'BLQ' will be displayed.

For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose measurements BLQ on Day 0, which will be imputed with zero for linear scale plots.

### 5.3.3 Sensitivity analysis

Not applicable.

### 5.3.4 Supplementary analyses

Not applicable.

## 5.4 Secondary Endpoint(s) Analysis

The secondary objective is to evaluate CZP exposure over a maximum of 24 weeks administration to adults with active RA and evaluate the safety of CZP in adults with active RA.

### 5.4.1 Key secondary endpoint(s)

The secondary variables will include the following endpoints.

- CZP plasma concentrations over duration of the study including Visit 2 till Visit 16 (70 Days through SFU visit).
- Treatment-emergent SAEs from first dose through the SFU Visit.
- Treatment-emergent AEs leading to withdrawal from first dose through the SFU Visit

#### 5.4.1.1 Definition of endpoint(s)

Key secondary endpoints will be to evaluate CZP plasma concentrations over the duration of study and treatment emergent SAEs and AEs leading to withdrawal from the time of the first CZP dose through the SFU Visit.

#### 5.4.1.2 Main analytical approach

##### 5.4.1.2.1 CZP plasma concentrations over the duration of study

Individual plasma concentrations of CZP (from conventional venous sampling) will be listed for PKS and will include the actual and nominal sampling times. Any samples that are obtained outside the tolerance window permitted at the specified time point will be discussed at the DEM and any

possible exclusion from any specific analyses (i.e. summary statistics table and geomean figure) will be documented accordingly. If deemed appropriate, the analyses of the summary stats table and geomean figure may be repeated with and without the specific samples affected.

The PK plasma concentrations of CZP will be summarized nominal sampling times by MTX use at screening (same definition in Section 6.1.1) using descriptive statistics (number of available observations (n), arithmetic mean, median, SD, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean (assuming lognormally distributed data)). Values below the LLOQ will be reported with a clear sign indicating that they were below the LLOQ.

Geometric mean profiles of plasma concentrations for CZP over time will be presented in both linear and semi-logarithmic scale. For the linear scale plot only, the lower and upper 95% confidence interval (CI) for the geometric mean will be displayed.

All plasma concentration figures will include the LLOQ on the semi-logarithmic scale plots and will be based on scheduled times and grouped by MTX use at screening.

Further PK data handling rules are described in Section 5.3.2 .

#### 5.4.1.2.2 Treatment-emergent SAEs

A treatment-emergent adverse event (TEAE) is defined as events that have a start date on or following the first administration of study treatment in RA0138 through the final administration of study treatment+70 days through SFU visit. The treatment-emergent serious adverse event (TESAE) will follow the same definition and also mark serious adverse event as “Yes” in the adverse events CRF form.

The analysis for secondary endpoint for treatment-emergent SAEs will be included as follows:

- Incidence of treatment-emergent SAEs
- Incidence of treatment-emergent SAEs by Maximum Intensity
- Incidence of treatment-emergent SAEs by Maximum Relationship

Serious AEs summaries will be ordered by alphabetical SOC , HLT and decreasing frequency of PT within SOC in the CZP column for tables including event counts.

A listing will be presented for SS for treatment-emergent SAEs . This will include the SOC, HLT and PT, onset date/time and outcome date/time of the event (including relative days), the AE duration, pattern of event, serious/intensity, relationship, action taken and outcome. In addition, the listing will flag hospitalization, SAEs, and AE of special interest.

#### 5.4.1.2.3 Treatment-emergent AEs leading to withdrawal

Similarly, the analysis for treatment emergent AEs leading to withdrawal from the time of the first CZP dose through the SFU Visit will be included as follows:

- Incidence of treatment emergent AEs leading to withdrawal
- Incidence of treatment emergent AEs leading to withdrawal by Maximum Intensity
- Incidence of treatment emergent AEs leading to withdrawal by Maximum Relationship

Treatment emergent AE summaries will be ordered by alphabetical SOC and decreasing frequency of PT within SOC in the CZP column for tables including event counts.

A listing will be presented for SS for treatment emergent AE leading to withdrawal and follow the same display of output as described in Section 5.4.1.2.2 . The other similar AE data handling rule will be also followed in Section 5.5.1.2.

#### 5.4.1.3 Sensitivity analysis

Not applicable.

#### 5.4.1.4 Supplementary analyses

Not applicable.

### 5.4.2 Supportive secondary endpoint(s)

Not applicable.

## 5.5 Tertiary/Exploratory Endpoint(s) Analysis

Tertiary/Exploratory Endpoint(s) analysis or Other Objects and Endpoints will be performed and consist of following objectives:

- To assess the occurrence of anti-CZP antibodies (utilizing the ECLIA method) over the duration of the study
- To assess the efficacy of CZP
- To evaluate other safety parameters

The endpoints will be as follows:

- ADAb screening status (positive or negative screen), confirmatory status (positive or negative immunodepletion), and the titer for "positive immunodepletion" samples at each scheduled assessment after first CZP dose through SFU
- Change in Routine Assessment of Patient Index Data 3 (RAPID3) from Baseline to Week 12
- TEAEs, vital signs, and laboratory assessments

The following section will present the endpoints except ECG which are described in Section 5.6.1.1.

.

#### 5.5.1.1 Immunological Analyses

Immunogenicity samples will be tested using the ECLIA method. Antibodies to CZP will be evaluated in plasma samples collected from all participants according to the Schedule of Activities.

Plasma samples will be screened for antibodies binding to CZP and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of CZP.

The incidence of immunogenicity will be summarized by visit, as specified and based on SS.

##### 5.5.1.1.1 Handling of dropouts or missing data

Levels of ADAb that are negative or no titer provided will be regarded as zero (negative) for all individual ADAb figures.

##### 5.5.1.1.2 Anti-drug antibodies

ADAb antibodies will be measured using a tiered assay approach: screening assay, confirmatory assay and titration assay. The ADA status at sample level will be defined in Table 5–1 .

A screening cut point will be determined by the bioanalytical laboratory that will be used to determine the status of ADAb as Positive Screen (PS) or Negative Screen (NS). Samples presenting ADAb levels PS are considered "potentially ADAb positive" and will be further evaluated in the confirmatory assay, the result of which will be reported as either "Positive Immunodepletion" (PI) or "Negative Immunodepletion" (NI). Confirmed positive samples (reported as PI) will be titrated, and the titer (reciprocal dilution factor including minimum required dilution) will be reported.

ADAb status at sample level:

**Table 5–1 : ADA status at Sample level**

| | |
|---|---|
| ADA positive (ADAb+) | Sample values that are 'positive screen' and 'positive immuno-depletion' |
| ADA negative (ADAb-) | Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' if corresponding drug levels are equal or below the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADA or limit dictated by the ADA assay and project needs (e.g. 250 ng/ml). |
| ADA inconclusive | Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' but with corresponding drug levels above the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADA or limit dictated by the ADA assay and project needs (e.g. 250 ng/ml) |
| Missing | Samples that were not collected per schedule or that could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc. |

Participant Classification:

- A participant will be classified as overall positive if at least one post Baseline measurement is ADAb+ (see definition above) (this includes participant who have negative and positive results at baseline)
- A participant will be classified as overall negative if at all post Baseline visits the ADAb status is negative (this includes study participants who have positive and negative results at Baseline)
- A participant will be classified as having classification of ADA status as stated in below Table 5–2 .

**Table 5–2 : Classification of ADA status**

| | | |
|---|---|---|
| 1. | Pre ADA negative and treatment-emergent ADA negative | Study participant who were negative at Baseline and negative at all sampling points post treatment at all timepoints |
| 2. | Pre ADA negative and treatment-(emergent) induced ADA positive | Study participant who were negative at Baseline and positive at any sampling point post treatment. This group also included study participants who had a missing pre-treatment sample (either missing or insufficient volume) with 1 or more positive post-treatment samples. |
| 3. | Pre ADA positive and treatment-emergent reduced ADA | Study participants who were positive at Baseline, and negative at all sampling points post treatment all timepoints. |
| 4. | Pre ADA positive and treatment-emergent unaffected ADA positive | Study participants who were positive at Baseline and were positive at any sampling point post treatment with titer values of the same magnitude as Baseline (i.e., less than a predefined fold difference from the Baseline value of 4.11). |
| 5. | Pre ADA positive and treatment-emergent ADA boosted positive | Study participant who were positive at Baseline and were positive at any sampling point post treatment with increased titer values compared to Baseline (greater than a predefined fold difference increase of 4.11 from Baseline value which is defined within the validation of the assay). |
| 6. | ADA inconclusive | Study participants who were positive at Baseline and some post-treatment samples were missing, while other post-treatment samples were negative. |
| 7. | Treatment emergent ADA positive | Combination of 2 and 5 |
| 8. | Pre-treatment ADA positive | Combination of 3, 4 and 5 |
| 9. | Missing | Study participants who were negative at Baseline or missing their Baseline assessment, were not positive at any post-Baseline visit, and have at least one missing post-treatment scheduled assessment. |



Analysis:

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant. All analyses will be run on the SS, unless specified otherwise. For all

tabulations, percentages will be calculated based on the number of study participants with non-missing data.

- Individual participant concentration-time profiles of CZP will be displayed graphically in linear and semi-logarithmic scale and grouped by MTX use at screening.
- All individual study participant-level ADAb results will be listed for all study participants. This will include the screening assay, confirmatory assay, and titer (if applicable).
- Summary table displaying the number and percentage of study participants with a positive ADA, negative ADA, inconclusive or missing ADA sample status at the time of each visit by treatment group. [Note that in case of presence of pre-ADA, no differentiation can be made between pre-ADA and treatment emergent ADA (either newly induced or boosted ADA). Note this table is not be used for incidence interpretation].
- Based on the overall ADA study participant classification above from Table 5-2, the following will be determined and presented: summary tables displaying the number and percentage of study participants in each of ADA participant status categories (1–9), with the denominator being the total number of study participants having an individual ADA participant category defined during the corresponding analysis period and treatment group. (All study participants will be assigned to a category in this table and should not be confused with ADA incidence that is defined below).

Incidence and prevalence:

- Total prevalence of pre-Ab overall and by treatment group. Total prevalence of pre-Ab: n/NN % number of participants that have a pre-ADA positive ADA sample status, with NN being the denominator defined as all participants having an evaluable baseline ADA sample.
- Overall ADA incidence and by treatment group. Treatment-Emergent Anti-CZP Antibody Positivity Activity for combined results of treatment-boosted ADA-positive participants and treatment induced ADA-positive participants. n/N % of participants that are treatment emergent, with N being the denominator defined as all participants except the participants categorized as inconclusive.
- Summary tables of the time point of the first occurrence of treatment emergent (TE) ADA positivity (i.e first ADA sampling time point with ADA positive status if participant is pre-ADA negative or first ADA sampling time point with fold difference increase from Baseline > the MSR if participant is pre-ADA positive) for study participants in category 2 and 5. The table will summarize the number and percentage of TE ADA positive participants who present first occurrence of TE ADA positivity at the specified time point and will include the cumulative number and cumulative percentage of participants at each time point. In case of ADA samples with missing or inconclusive status before the first ADA sampling time point considered TE ADA positive, the time point of the first occurrence of TE ADA positivity will be reported as ≤ than the respective ADA time point. In case of pre-ADA present in more than 10% of the study participants, the table is split out between ADA participant category 2 and 5. The denominator for % calculations will be the total number of TE ADA positive participants.
- Number and percentage of study participant Baseline Anti-CZP status and Treatment-Emergent Anti-CZP Antibody Status will be summarized during the entire study. The change in category from Baseline ADAb status including ADAb-, ADAb+, Missing and total will be presented in

shift tables at each post-Baseline treatment treatment-emergent anti-CZP antibody status. Treatment Treatment-Emergent Anti-CZP Antibody Status will be categorized as below:

- Negative : Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb-
- Positive <512 : Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb+ and ADAb titer is less than 512.
- Positive 512-<=1024: Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb+ and ADAb titer is greater than 512 and less than or equal to 1024.
- Positive>1024: Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb+ and ADAb titer is greater than 1024.
- Any positive : Study participants having treatment-emergent ADAb+.
- Total : total Treatment Treatment-Emergent Anti-CZP Antibody Status

- Number and percentage of study participant Anti-CZP titer by visit will be summarized during the entire study. ADAb titer will be categorized as below:
  - Negative : The ADAb status is ADAb-
  - <=32 : The ADAb titer result is less than or equal to 32.
  - >32-128: The ADAb titer result is greater than 32 and less than or equal to 128.
  - >128-512: The ADAb titer result is greater than 128 and less than or equal to 512.
  - >512-1024: The ADAb titer result is greater than 512 and less than or equal to 1024.
  - >1024-4096: The ADAb titer result is greater than 1024 and less than or equal to 4096.
  - >4096: The ADAb titer result is greater than 4096.

A listing will be presented showing the CZP concentrations and ADAb measurements in the same output in adjacent columns, based on the SS. The listing will include the CZP concentration and ADAb status (positive or negative) and screening assay results (PS or NS) and confirmatory assay results if applicable (NI or PI), together with the titer if applicable. In addition, the time since the administration of study medication will be reported (in days). ADAb samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged.

Time course plots of all individual CZP plasma concentrations profiles (each participant corresponding to a line) (spaghetti plot) with identification of the individual ADA participant category using different colors ( categories 1, 3,4 and 7. If not sufficient participants in category 3 and 4, these could be combined for this plot). These plots will be produced on a linear and semilogarithmic scale and multi-panel per treatment group. Individual samples with positive ADA sample status will be visualized using a symbol or a red dot. Dosing nominal time points should be indicated below the x-axis. A similar plot may be considered for PD endpoints. The plot may be stratified based on MTX use at baseline/screening.

Finally, individual participant plots will be presented displaying the ADAb titer and CZP concentrations overlaid on the same figure. The figure will also show the timing and dose of each administration of CZP received during the study. The ADAb data will be plotted using a semi-logarithmic scale. ADAb samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged on the plot.

The rules for handling values that are BLQ in the CZP concentration data are described in Section 5.5.1.1.1. For the ADAb data, any negative results for which there are no titers (as applicable) available at a specific visit will be substituted with 0.001 for the purpose of the figure.

### 5.5.1.2 RAPID3 analysis

The MDHAQ items that make up the RAPID3 (Routine Assessment of Patient Index Data 3) will be assessed at Baseline and Week 12. The MDHAQ is derived from the HAQ, and the sections that will be utilized are the following:

- MDHAQ-FN : Physical function listed in 10 activities; converted to a scale from 0 to 10 for the RAPID3 score
- MDHAQ-PN : Pain assessed as 0.5 increments from 0 to 10
- MDHAQ-PTGL : Patient's global status assessed as 0.5 increments from 0 to 10
- RAPID3 cumulative score is calculated as the sum (0 to 30) of FN, PN, and PTGL.

RAPID3 analysis will be based on the SS population. By participant list of the MDHAQ-FN (converted scale), MDHAQ-PN, MDHAQ-PTGL and RAPID3 cumulative score with actual values and change from Baseline will be provided at Baseline and Week 12.

### 5.5.1.3 Adverse Events

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded and categorized by relationship to CZP. The definitions of TEAE can be found in Section 5.4.1.2.2.

The number and percentage of study participants who experience TEAEs will be for all study participants, SOC, and PT, based on the SS (unless otherwise stated).

Summaries of TEAEs will include the following:

- Summaries of TEAEs will include the following:
    - Incidence of TEAEs (overview including number and percentage of study participants with any TEAEs, serious TEAEs, discontinuations due to TEAEs, drug related TEAEs, severe TEAEs and deaths; event counts will also be included)
- Incidence of TEAEs
- Incidence of TEAEs by maximum relationship
- Incidence of TEAEs by maximum intensity
- Incidence of non-serious TEAEs above threshold of 5% of study participants
- Incidence of non-serious TEAEs above threshold of 5% of study participants by Relationship

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates, see Section 6.1.6.2) to suggest that the AE started prior to dosing.

Summary tables will contain counts of study participants, percentages of study participants in parentheses and the number of events. A participant who has multiple events in the same SOC and PT will be counted only once in the participant counts, but all events will be included. For the summary of injection site reactions, the specific PTs to be included will be reviewed and documented at the DEM.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Study participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

In summaries including relationship to CZP, the following relationships will be summarized: 'Not related', 'Related'. Study participants who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship (for CZP) will be considered as 'Related' for the tabulations but recorded as missing in the listings.

A listing will be presented for SS for AEs including TEAE and non-TEAE. This listing will follow the same structure as described in Section 5.4.1.2.2.

### 5.5.1.4 Vital Signs

#### 5.5.1.4.1 Vital Sign Values Over Time

The following vital signs measurements will be collected at Screening visit and End of Study visit (SFU/EDV):

- Pulse rate (bpm)
- Systolic and diastolic blood pressure (mmHg)
- Oral Temperature (°F or °C)
- Respiratory rate (breaths per minute)

Descriptive statistics will be reported for all vital sign for SS. Measured values and changes from Baseline will be summarized by vital signs variables and time point(screening and SFU). Summarization will be as treated, and study participants who missed treatments will not be summarized.

#### 5.5.1.4.2 Individual Participant Changes of Vital Sign Values

A by- participant listing of all vital sign measurements and change from Baseline will be presented for all study participants and time point. Body weight will be included in the listing.

#### 5.5.1.5 Clinical laboratory evaluations

##### 5.5.1.5.1 Handling of dropouts or missing data

Measurements below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the lab purpose of calculating change and percentage change from Baseline for summaries and figures. Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper limit of quantification.

Descriptive statistics will be calculated if at most 33% of the individual data points at a time point (Visit 13, Week 12 and SFU) are missing or are either not quantifiable (<LLOQ) or ALQ. The denominator for percentages will be based on the number of study participants at corresponding analysis visit for the purpose of the safety analysis. Unscheduled and additional laboratory results will not be summarized but only listed.

##### 5.5.1.5.2 Laboratory values over time

Laboratory data (clinical chemistry, hematology, urinalysis and other screening test) and changes from Baseline (if applicable) for numeric variables will be listed for SS and time point. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 5.5.1.5.1 . Values outside the reference range for the numeric variables will be flagged in the listings. The reference ranges will also be reported in the listings.

Chemistry and hematology parameters will be summarized on the SS at each time point, for both absolute values and changes from Baseline.

Laboratory variables will be grouped according to the laboratory function panel and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory.

Liver function test elevations should be listed. Potential Hy's Law is defined as a participant with (AST or ALT > 3 x ULN) and TBL > 2 x ULN and ALP < 2 x ULN on the same visit.

In order to meet the above criteria, a participant must experience the elevation in bilirubin and ALT or AST at the same visit. For example, a participant who experiences a >=2 x ULN elevation of bilirubin at one visit and a 3 x ULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria.

Markedly abnormal laboratory values will generally be defined as those categorized as Grade 3 or higher based on the Rheumatology Common Toxicity Criteria (RCTC) v2.1 (Woodworth et al, 2007). Definitions of markedly abnormal values using the Grade 3 cutpoints are given in the tables below (Table 5–3 for markedly abnormal hematology values and Table 5–4 for markedly abnormal biochemistry values). Any ambiguity about the RCTC criteria was resolved by correspondence with the senior author. In particular, the published Grade 3 cutpoint for lymphocytes (<1.0) was found to be too high, corresponding with the lower limit of normal, and thus was changed to <0.5.

Markedly abnormal laboratory (hematology and biochemistry) values with abnormality flag and Hy's Law will be flagged in laboratory listing together for SS and each time point.

**Table 5–3 Definitions of Markedly Abnormal Hematology Values**

| Parameter (SI units) | Markedly Abnormal Definition | |
|---|---|---|
| | Low | High |
| Hemoglobin (g/L) | < LLN<br>AND decrease from Baseline>20 | N/A |
| Hemoglobin (g/L) | <80 | N/A |
| Leukocytes (total x 1000) | <2.0 | N/A |
| Lymphocytes (x 1000) | <0.5 | N/A |
| Neutrophils (x 1000) | <1.0 | N/A |
| Platelets (x 1000) | <50 | N/A |

N/A = Not Applicable

**Table 5–4 Definitions of Markedly Abnormal Biochemistry Values**

| Parameter (SI units) | Markedly Abnormal Definition | |
|---|---|---|
| | Low | High |
| Alkaline Phosphatase | N/A | >3 x ULN |
| ALT | N/A | >3 x ULN |
| AST | N/A | >3 x ULN |
| Calcium (mmol/L) | <1.75 | >3.125 |
| CPK | N/A | >4 x ULN |
| Creatinine | N/A | >1.8 x ULN |
| Glucose (mmol/L) | <2.22 | >13.89 |
| Potassium (mmol/L) | <3.0 | >6.4 |
| Sodium (mmol/L) | <125 | N/A |
| Total bilirubin | N/A | ≥2 x ULN |
| Uric acid | N/A | ≥3 x ULN |

N/A = Not Applicable

Unscheduled visit and duplicate measurement will be handled in Section 6.1.6.1 and baseline definition will be described in Section 5.1.1.1.5.



#### 5.5.1.5.3 Individual Participant Changes of Laboratory Values

For selected laboratory variables that are identified in Section 5.5.1.5.2 , the change in category from Baseline will be presented in shift tables at each post-Baseline assessment.

## 5.6 (Other) Safety Analyses

Other safety will be assessed using the SS. All safety endpoints will be analyzed using descriptive statistics. Safety summaries will include presentations of extent of exposure, and additional safety assessments including ECG and physical examination. For safety analysis, unscheduled visit and duplicate measurement will be handled in Section 6.1.6.1 and baseline definition will be described in Section 5.1.1.1.5.

### 5.6.1 Extent of Exposure

The number of injections, total doses received, and total duration of exposure will be summarized for SS with continuous statistics (eg, mean, std, median).

Duration of exposure to study medication will be calculated as:

- Date of last administration of study medication – date of first administration + 14 days

Time at risk (days) will be calculated as:

- Date of last administration of study medication – date of first administration + 70 days.

In addition, all IMP administration details (including date/time of administration, dose), where to perform injection (home or study site), who to perform the injection (study participant or site personnel), injection site (arm , abdomen or thigh), side of body (left or right),volume, injection speed (fastest-8 seconds, fast-11 seconds, slow-14 seconds and slowest-17 seconds ) will be listed using the SS. All dosing records including self-injection at Week 14, 16, 20 and 22 with no specific visit label will also be listed and considered into exposure summary.

#### 5.6.1.1 Electrocardiograms

Standard 12-lead ECG recordings will be taken with the participant resting in the supine position for at least 5 minutes and will be presented in SS.

#### 5.6.1.2 Electrocardiogram Values Over Time

As ECG is only collected at Screening visit based on schedule of activities.

The following variables will be reported:

- Heart rate
- RR interval
- PR interval
- QRS duration
- QT interval
- QT interval corrected for heart rate (Bazett's formula)

Measured values will be summarized for each variable for all study participants at screening visit.

Electrocardiogram findings will be listed separately.

#### 5.6.1.2.1 Individual Participant of Electrocardiograms Values

The results of all ECG variables will be reported in the by-participant listings. The listing will be presented for ASP at screening visit. All participants who may have clinically significant electrocardiogram (ECT) abnormalities at screening will be presented.

### 5.6.2 Additional Safety Assessments

#### 5.6.2.1 Other safety endpoint(s)

#### 5.6.2.1.1 Physical examination

Study participants with abnormalities in the physical examination will be listed including details of the abnormality and based on SS.

#### 5.6.2.1.2 Additional Laboratory Tests

In this study, details of all pregnancies in female participants will be collected after the start of study treatment and until SFU Visit and listed in additional laboratory test. In addition, other screening tests results also include serum or urine alcohol and drug screen and will be listed for SS.

## 5.7 Other Analyses

### 5.7.1 Other endpoints and/or parameters

#### 5.7.1.1 Pharmacokinetics

Pharmacokinetic samples will be tested using the ECLIA method. All PK assessments will be evaluated as described in the Section 5.3.

#### 5.7.1.2 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

#### 5.7.1.3 Genomics

Genomics will not be evaluated in this study.

#### 5.7.1.4 Tuberculosis screening (IGRA) and Tuberculosis Questionnaire

TB test data at Screening period and TB questionnaire at Week 12 and Week 24 be listed on the SS.

#### 5.7.1.5 COVID-19 Impact

For study participants impacted by the COVID-19 global pandemic, data was collected on a separate eCRF. This form was collected for study visits that were affected by COVID-19, and it collected how the visits were impacted by the pandemic (e.g., performed out of window, done by telephone instead of on-site, not done, etc).

Based on how the visit was affected by the global pandemic, all visits will have following impact categories indicating how the visit was performed:

- Visit not done
- Visit performed out of window
- Home visit
- Missed study drug
- Administration/dispensation
- Temporary discontinuation of study drug
- Termination of study participation
- Other (if other ,specify the details)

Additionally, for visits that are affected by COVID-19, all assessments that are missing will be flagged as missing due to COVID-19. Further, the specific reason of missing data will be captured as the following flags:

- Confirmed COVID-19 infection
- Suspected COVID-19 infection
- General circumstances around COVID-19 without infection
- Other

A summary of number and percentage of study participants with COVID-19 impact for all study participants and visit will be provided for the ASP.

A by-site, participant and visit listing of COVID-19 related protocol deviations will be provided including impacted visit and date of impacted visit.

## 5.8 Subgroup analyses

Not applicable.

## 5.9 Interim Analyses

No interim analysis is planned.

## 5.10 Data Monitoring Committee (DMC) or Other Review Board

No data monitoring is planned.

# 6 SUPPORTING DOCUMENTATION

## 6.1 Appendix 1 Non-key analysis specifications

### 6.1.1 Baseline characteristics and demographics

A by- participant listing of Baseline demographics will be presented for ASP. This will include the participant number, year of birth (if available), age (in years), country, sex, race, ethnicity, height

(in cm), weight (in kg at screening and at pre-dose) and body mass index (BMI). The age will be directly entered into the study database and will not be re-calculated for the statistical analysis. Concomitant MTX use will also be presented and include:

- With MTX use at screening
- Without MTX use at screening

As study participants may take concomitant methotrexate (MTX) during the study, a minimum of 8 study participants must be enrolled who are not on concurrent administration of MTX, so at least 8 study participants will be expected for subgroup of "without MTX use at screening". In addition, the non-MTX study participant may start to take MTX after Week 12, Day 84 where a study participant not on MTX at screening. The MTX user subgroup above will be only based on MTX status at screening status, even if a study participant enrolled to study as non -MTX user but then used an MTX after Week 12, this study participant will be still classified into "without MTX use at screening".

All demographic characteristics obtained at the Screening visit and at pre-dose visit for weight will be summarized for the SS and the ASP (apart from the date of birth).

Body mass index in kg/m2 is calculated based on the height (in m) and the weight (in kg) using the following formula:

BMI (kg/m2) = weight (kg)/[height (m)]2

The BMI will be reported to 1 decimal place.

For the EudraCT reporting, the age categories will include

- 18 to <65 years
- 65 to <85 years
- ≥85 years

For the clinicaltrials.gov reporting, the age categories will include:

- ≤18 years
- 19 to <65 years
- ≥65 years

Childbearing potential will be listed by all study participants screened.

### 6.1.2 Protocol deviations

Important protocol deviations (IPDs) will be identified and classified by the deviation types identified in the IPD document.

Important protocol deviations will be summarized for all study participants (ASP) to include number and percentage of participants with

1) No important protocol deviations
2) At least one protocol deviation and the
   - Inclusion criteria deviation
   - Exclusion criteria deviation

- Withdrawal criteria deviation
- Prohibited concomitant medication use
- Incorrect treatment or dose
- Treatment non-compliance

3) Exclusion from the PKS (and all categories in item 2 above).

A by-participant listing of important protocol deviations will be provided using the SS.

A by-site participant listing of COVID-19 related important protocol deviations will be provided using the SS.

### 6.1.3 Medical history

Medical history will be listed and summarized for the SS and will include the MedDRA version 23.1 system organ class (SOC) and preferred term (PT). Procedure history will be listed separately from the medical history including date of procedure and relationship with RA based on the SS. Similarly, concomitant medical procedure will be also listed separately including date of procedure and procedure primarily relationship based on the SS. For study participants with DILI events, hepatic events supplemental medical history and relevant data (potentially hepato-toxic medication, symptoms of hepatitis and symptoms of hypersensitivity) for study participants with suspected DILI event will be listed with liver function laboratory results.

### 6.1.4 History of Rheumatoid Arthritis

The study participants' history of RA will be summarized on the SS and listed. The following RA history variables will be included:

- Presence of extra-articular features (ever had and present at Screening)
- Duration of RA (first persistent symptoms). Duration of RA should be calculated as the difference between screening date and first persistent symptoms. If the date of diagnosis is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing). Sometimes Baseline date is used instead of Screening date.
- Duration of RA (since date of diagnosis). Duration of RA should be calculated as the difference between screening date and date of diagnosis. If the date of diagnosis is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing). Sometimes Baseline date is used instead of Screening date.
- Duration category of RA since first diagnosis (typically < 2 years and ≥ 2 years, but other cutpoints may be used depending on the study).
- Duration of RA (years) will be calculated as:
  - Duration of RA (first persistent symptoms)= (screening date - first persistent symptoms)/365.25
  - Duration of RA (since date of diagnosis)=(screening date - date of diagnosis)/365.25.

History of rheumatoid arthritis will be listed for the SS for all study participants including date of first persistent symptoms of RA, date of first diagnosis, history or current of extra-articular features (keratoconjunctivitis sicca (yes/no), rheumatoid nodules(yes/no), scleritis(yes/no), neuropathy(yes/no), vasculitis(yes/no), pulmonary fibrosis(yes/no), other ).

### 6.1.5 Prior/concomitant medications

#### 6.1.5.1 Prior medication definition

Prior medications include any medications that started prior to the start date of study medication. If a participant takes a medication before the date of administration of IMP, this medication will be classified as 'prior medication'. With this definition, any medication recorded that has been taken for at least 1 day before the date of administration of IMP will be considered as prior. This includes medications that started prior to dosing and continued after.

#### 6.1.5.2 Concomitant medication definition

Concomitant medications are medications taken at least one day in common with the study medication dosing period. For Cimzia, the dosing period is typically from the date of first dose up to (but not including) 14 days post last dose. Thus, a concomitant medication is any medication whose start date is prior to the date of last study medication administration + 14 days, and whose stop date is either missing, or on or after the date of first study medication administration.

From the definitions above, any medication that started prior to dosing and continued after dosing will be classified as both prior and concomitant.

Any medications with missing dates and/or times will be handled as described in Section 6.1.6.2 in order to classify them as prior or concomitant.

Prior and concomitant medications will be listed and summarized, separately, for the SS for all study participants by WHODD version Sep/2020 B3 update Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3], preferred term (PT) and reported term (listing only).

Separate tabulations will be presented for the following:

- Prior medications
- Concomitant medications

All medications will be listed including glossary and will include coding information, reported term, dose per intake and unit, frequency, formulation, route of administration, indication, category (prior/concomitant) and start and end date (or ongoing, if applicable).

### 6.1.6 Data derivation rules

#### 6.1.6.1 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings. Repeated and unscheduled measurements will not be used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, or the repeated measurement occurred prior to Investigational Medicinal Product (IMP) administration and is defined as the 'baseline'. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the first dose of IMP the latest reliable value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics
- For repeated measurements obtained at the designated Baseline visit, the latest reliable value (which may be scheduled or unscheduled) will be defined as the Baseline. Repeated measurements designated Baseline will be used in descriptive statistics rather than the planned measurement they replace
- For repeated measurements obtained at any time point after the first dose of IMP, the first reliable value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics.

#### 6.1.6.2 Handling of Dates and times

Partial dates may be imputed for the following reasons:

- Classification of adverse events (AEs) as treatment-emergent AEs
- Classification of medications as prior or concomitant
- Durations of AEs.

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial start dates/times:

If time is not collected for a certain domain, time will not be imputed for that domain.

- If only start month and year are specified and not the same as month and year of dosing then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00 h;
- If only the month and year are specified and the month and year of dosing is the same as the month and year of the start date, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use the 1st of the start month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of dosing then time will be imputed as the start time of the sc injection (ie, event will be regarded as treatment-emergent);
- If only the year is specified, and the year of dosing is not the same as the year of the start date then use January 01 of the year of the start date. If time is missing this will be imputed as 00:00 h;
- If only the year is specified, and the year of dosing is the same as the year of the start date, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the start date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of dosing then time will be imputed as the start time of the sc injection (ie, event will be regarded as treatment-emergent);
- If the start date is completely unknown, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of dosing then time will

be imputed as the start time of the sc injection (ie, event will be regarded as treatment-emergent).

Any medication with a start date on the dosing date and time unknown, will be assumed to be concomitant.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month;
- If only the year is specified, then use December 31 of the known year;
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing date and/or times will be imputed as described in Table 6–1 for the calculation of duration of each AE. Adverse event duration is computed in and reported in day and time format: xx d hh:mm.

**Table 6–1: Calculation rules for duration**

| Data availability | Onset date/time | Outcome date/time | Calculation rules |
|---|---|---|---|
| Complete data | D1/T1 | D2/T2 | Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d |
| End time missing | D1/T1 | D2/-- | End time is substituted by time 23:59h (=23.98 in decimal format)<br>Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d |
| Start time missing | D1/-- | D2/T2 | Onset time is substituted by time 00:00h.<br>Note: if onset date is on the same date of first study administration, then the time point of first study administration will be used for missing onset time.<br>Duration ≤ [(D2 – D1)*24 + T2] / 24 d |
| Start and end time missing | D1/-- | D2/-- | Duration = <D2 – D1 + 1 |
| Start day and time missing | --/-- | D2/T2 | Duration = <[(D2 – D0)*24 + (T2 – T0)]/24 d<br>For a participant in the SS, D0 and T0 are the date and time of dosing and for screen failures, D0 is the date of the screening visit and T0 = 00:00h |
| End day and time missing | D1/T1 | --/-- | For ongoing AE:<br>Duration = >Discharge day – D1 d OR<br>For resolved AE:<br>Duration = <Discharge day – D1 d OR<br>Where discharge refers to the date of the end of study visit for completed study participants or the date of discontinuation for study participants that were withdrawn.<br>For any AEs with known start date/time after the date of discontinuation, the date of last contact will be used as the discharge day. |

**Table 6–1: Calculation rules for duration**

| Data availability | Onset date/time | Outcome date/time | Calculation rules |
|---|---|---|---|
| Start and end date missing | --/-- | --/-- | For ongoing AE:<br>Duration = >Discharge day – D0 d OR<br>For resolved AE:<br>Duration = <Discharge day – D0 d OR<br>For a participant in the SS, D0 and T0 are the date and time of dosing and for screen failures, D0 is the date of the screening visit and T0 = 00:00h.<br>Discharge refers to the date of the end of study visit or the date of discontinuation for study participants that were withdrawn.<br>For any AEs with known start date/time after the date of discontinuation, the date of last contact will be used as the discharge day. |

SS=Safety Set; IMP=investigational medicinal product.

### 6.1.7 AEs of Special Interest (AESIs)

An AE of special interest is defined as following events:

- Hy's Law (as described in Section 5.5.1.5.2)
- Serious infections, including opportunistic infections.
- Malignancies, including lymphoma.
- Serious cardiovascular events - also called Major Adverse Cardiac Events (MACE)
- Congestive heart failure.
- Demyelinating-like disorders.
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia.
- Serious bleeding events.
- Lupus and lupus-like syndrome.
- Serious skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrosis, and erythema multiforme).

Subsets on Adverse Events of Special Interest (AESIs) will either be extracted via Structured MedDRA Query (SMQ), via other automated queries based on search criteria specified by UCB or via manual medical review from the set of TEAEs or serious TEAEs.

Some types of AESIs are identified manually. For those, textual reporting in the CSR is deemed sufficient and no additional summary tables need to be generated. For others, especially those with automated search criteria additional TEAE summary tables are planned.

All manual searches and reviews have to be occurred prior to data cleaning meeting(DCM) and data evaluation meeting (DEM). A final review after database lock will be also executed in the framework of the data cleaning and data evaluation meeting.

The MedDRA SMQ terms are based on MedDRA version 23.1. In case that later MedDRA versions will be used, the appropriateness and spelling of the terms need to be reviewed and adapted accordingly.

The following summary tables will be produced for AESIs:

- TEAEs by SOC, HLT and PT for AESIs along with number and percentage summary
- Serious TEAEs by SOC, HLT and PT for AESI along with number and percentage summary

All AESIs the term(s) for extraction are specified in Table 6–1:

**Table 6–1:Adverse Events of Special Interest (AESIs)**

| AESIs term and other AE subsets | Extraction way | Term of SMQ (for SMQ extraction only) or other search strategy |
|---|---|---|
| AESIs: Infections, including serious opportunistic infections and tuberculosis | 1) Serious infections | |
| | 2) Opportunistic infections including tuberculosis, manual | 2) UCB defined search criteria for opportunistic infections including Tuberculosis |
| AESIs: Malignancies, including lymphoma | 1) SMQ<br>2) SMQ | 1) SMQ=”Malignant or unspecified tumours”<br>2) SMQ=”Malignant tumours”<br>Note: Non melanomic skin cancer will also be summarized by using HLT= “Skin neoplasms malignant and unspecified (excluding melanoma)” |
| AESIs: Congestive heart failure | 1) Congestive heart failure, manual | |
| | 2) Major adverse cardiovascular events (MACE) | 2) UCB defined search criteria[1)] |
| AESIs: Demyelinating-like disorders | SMQ | SMQ = “Demyelination (SMQ)” |

| AESIs term and other AE subsets | Extraction way | Term of SMQ (for SMQ extraction only) or other search strategy |
|---|---|---|
| AESIs: Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia | SMQ | SMQ=”Haematopoietic cytopenias” on subset of serious TEAEs |
| AESIs: Serious bleeding events | SMQ | SMQ=”Haemorrhages” on subset of serious TEAEs |
| AESIs: Lupus and lupus-like syndrome | Manual | Medical review of TEAE table |
| AESIs: Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme) | Manual | Medical review of serious TEAE table |

1) Will include fatal and serious non-fatal myocardial infarctions, cerebrovascular events and congestive heart failures based on MedDRA terms and medical reviews.

### 6.1.8 Potentially Clinically Significant Criteria for Safety Endpoints

Not applicable.

### 6.1.9 Compliance

At each visit after study medication is dispensed, participants must return all unused study medication and empty study medication containers. Drug accountability must be done in the participant’s presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen.

The compliance will be provided via drug accountability CRF form. No summary table will be provided for drug accountability, However, a by-participant listing of drug accountability including visit dispensed, kit number, and counter for RTSM integration (misallocation of drug kit) will be provided using the SS.

## 6.2 Appendix 2: Changes to Protocol-Planned Analyses

Not applicable.

# 7 REFERENCES

1. UCB Guideline: Guideline on performing NCA analysis, Nov 2017

2. Phillips, A. and Haudiquet, V. (2003), ICH E9 guideline 'Statistical principles for clinical trials': a case study. Statist. Med., 22: 1-11. doi:10.1002/sim.1328
3. Food and Drug Administration. Guidance for Industry. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs —General Considerations. US Dept of Health and Human Services, Center for Drug Evaluation and Research. Biopharmaceutics. March 2017.
4. EMEA/CHMP/BMWP/42832/2005 Rev. 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non -clinical and clinical issues , 18 Dec 2014.
5. CPMP/EWP/QWP/1401/98 Rev. 1/Corr Guideline on the investigation of bioequivalence (EMEA), 20 January 2010.
6. Health Canada Guidance, Conduct and Analysis of Comparative Bioavailability Studies, 8 Jun 2018.
7. Health Canada Guidance, Comparative Bioavailability Standards: Formulations use for Systemic Effects, 8 Jun 2018.

8.

# 8 APPENDICES

## 8.1 RAPID3 Assessment

The RAPID3 includes a subset of core variables found in the Multi-dimensional HAQ (MDHAQ). The MDHAQ, shown here, includes an assessment of physical function (Section 1 of the RAPID3 assessment [below]), a patient global assessment for pain (Section 2 of the RAPID3 assessment [below]), and a patient global assessment for global health (Section 3 of the RAPID3 assessment [below]). RAPID3 scores are quickly tallied by adding subsets of the MDHAQ as follows:

[redacted]

### How to calculate RAPID3 scores

1. Ask the patient to complete questions 1, 2, and 3 while in the waiting room prior to his/her visit.
2. For question 1, add up the scores in questions a to j only (questions k to m have been found to be informative, but are not scored formally). Use the formula in the box on the right to calculate the formal score (0 to 10). For example, a patient whose answers total 19 would score a 6.3. Enter this score as an evaluation of the patient's functional status.
3. For question 2, enter the raw score (0 to 10) in the box on the right as an evaluation of the patient's pain tolerance.
4. For question 3, enter the raw score (0 to 10) in the box on the right as an evaluation of the patient's global estimate.
5. Add the total score (0 to 30) from questions 1, 2, and 3 and enter them as the patient's RAPID3 cumulative score. Use the final conversion table to simplify the patient's weighed RAPID3 score. For example, a patient who scores 11 on the cumulative RAPID3 scale would score a weighed 3.7. A patient who scores between 0 and 1.0 is defined as near remission; 1.3 and 2.0 as low severity; 2.3 and 4.0 as moderate severity; and 4.3 and 10.0 as high severity.

## 8.2 SAP Amendment 1

### Rationale for the amendment

The main purposes of this amendment were:

- General update to analyses following Data Evaluation Meetings.
- To implement anti-drug antibody additional analyses.

### Modifications and changes

**Specific changes**

**Change #1**

**Section 5.1 General Considerations**

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using statistical analysis system (SAS®, SAS Institute, Cary, NC, US) version 9.3 or higher using validated program code according to relevant standard operating procedures.

**Has been changed to:**

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using statistical analysis system (SAS®, SAS Institute, Cary, NC, US) version 9.3 or higher using validated program code according to relevant standard operating procedures. **PK parameters will be calculated by Non-Compartmental Analysis (NCA) methods from the concentration-time data with actual time using Phoenix® WinNonlin® Version 8.3 or higher following UCB guideline: Guideline on performing NCA analysis , Nov 2017.**

**Change #2**

**Section 5.1.1.1.3 Study periods**

The duration of the study for each study participant is approximately 38 weeks.; consisting of the following 3 periods:

Screening Period ( up to 28 days): Visit 1, Day -28 to Day -1

Treatment Period (24 weeks) including Baseline visit: based on the first planned treatment starting from Visit 2 at Day 0 to the last planned treatment on Visit 15 at Day 168 (Week 24)

- 400mg loading dose phase for doses at Week 0, Weeks 2 and 4 followed by 200mg Q2W maintenance dose phase thereafter (at Week 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24)
- PK profile treatment Period: Day 72±6 hours to Day 80±6 hours. These visits may be conducted at home vist.

Safety Follow-Up: The end of study visit will be performed on 70 days after last IMP through SFU visit.

The end of the study is defined as the date of the last visit of the last study participant in the study. Study participants are considered to have completed the study if they complete the last scheduled study visit, not including safety follow-up visits. The safety follow-up visit is 70 days post last dose. If study participants are continuing onto commercial Cimzia, the safety follow-up is 30 days post last dose.

**Has been changed to:**

The duration of the study for each study participant is approximately 38 weeks.; consisting of the following 3 periods:

Screening Period ( up to 28 days): Visit 1, Day -28 to Day -1

Treatment Period (24 weeks) including Baseline visit: based on the first planned treatment starting from Visit 2 at Day 0 to the last planned treatment on Visit 15 at Day 168 (Week 24)

- 400mg loading dose phase for doses at Week 0, Weeks 2 and 4 followed by 200mg Q2W maintenance dose phase thereafter (at Week 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24)
- PK profile treatment Period: Day 72±6 hours to Day 80±6 hours. These visits may be conducted at home visit.

Safety Follow-Up: The end of study visit will be performed on 70 days after last IMP through SFU **visit**.

The end of the study is defined as the date of the last visit of the last study participant in the study. Study participants are considered to have completed the study if they complete the last scheduled study visit**(Screening, Baseline Visit, Treatment Period [through Week 24], and SFU).** The safety follow-up visit is 70 days post last dose. If study participants are continuing onto commercial Cimzia, the safety follow-up is 30 days post last dose.

**Change #3**

**Section 5.1.1.1.4 Mapping of assessments performed at Early Discontinuation Visit**

For example, suppose the patient also discontinues at Day 176 ( in the midpoint of Week 24, Day 168 and Week 12, Day 84), then the Week 12, Day 84 will be assigned and firstly considered. However, if there was recently assessed at Week 12, the assessments obtained at premature termination visit should be re-mapped and analyzed at the Week 24 visit, as there is already valid data available at the Week 12 visit.

**Has been changed to:**

For example, suppose the patient also discontinues at Day **126** ( in the midpoint of Week 24, Day 168 and Week 12, Day 84), then the Week 12, Day 84 will be assigned and firstly considered. However, if there was recently assessed at Week 12, the assessments obtained at premature termination visit should be re-mapped and analyzed at the Week 24 visit, as there is already valid data available at the Week 12 visit.

**Change #4**

**Section 5.1.1.2 Protocol Deviations**

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual study participant.

**Has been changed to:**

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual study participant. **PK samples outside the protocol windows, missing doses or delayed doses potentially impacting PK, will be reviewed. PK sampling protocol deviations will not automatically cause their exclusion from the PKS set. The table of summary PK statistics and geometric mean PK concentration-time figure will be presented with and without those PK samples determined to be protocol deviations.**

**Change #5**

**Section 5.3.2 Main analytical approach**

The following rules will apply for the PK data summaries:

- Values below the LLOQ will be reported as BLQ for individual data and will be substituted with LLOQ/2 for the descriptive statistics

**Has been changed to:**

The following rules will apply for the PK data summaries:

- **PK parameters are reported with 3 significant digits and Descriptive statistics reported to 4 significant figures for the mean, median and standard deviation (SD) and to 3 significant figures for all others.**

- Values below the LLOQ will be reported as BLQ for individual data and will be substituted with LLOQ/2 for the descriptive statistics

**Change #6**

**Section 5.4.1.2.1 CZP plasma concentrations over the duration of study**

Individual plasma concentrations of CZP (from conventional venous sampling) will be listed for PKS and will include the actual and nominal sampling times. Any samples that are obtained outside the tolerance window permitted at the specified time point will be discussed at the DEM and any possible exclusion from analysis will be documented accordingly.

**Has been changed to:**

Individual plasma concentrations of CZP (from conventional venous sampling) will be listed for PKS and will include the actual and nominal sampling times. Any samples that are obtained outside the tolerance window permitted at the specified time point will be discussed at the DEM and any possible exclusion from **any specific analyses (i.e. summary statistics table and geomean figure) will be documented accordingly. If deemed appropriate, the analyses of the summary stats table and geomean figure may be repeated with and without the specific samples affected.**

**Change #7**

**Section 5.4.1.2.1 CZP plasma concentrations over the duration of study**

The other similar PK data handling rule will be also followed in Section 5.3.2 .

**Has been changed to:**

All plasma concentration figures will include the LLOQ on the semi-logarithmic scale plots and will be based on scheduled times and grouped by MTX use at screening.

**Further** PK data handling **rules are described** in Section 5.3.2 .

**Change #8**

**Section 5.5.1.1.2 Anti-drug antibodies**

ADAb antibodies will be measured using a tiered assay approach: screening assay, confirmatory assay and titration assay.

A screening cut point will be determined by the bioanalytical laboratory that will be used to determine the status of ADAb as Positive Screen (PS) or Negative Screen (NS). Samples presenting ADAb levels PS are considered "potentially ADAb positive" and will be further evaluated in the confirmatory assay, the result of which will be reported as either "Positive Immunodepletion" (PI) or "Negative Immunodepletion" (NI). Confirmed positive samples (reported as PI) will be titrated, and the titer (reciprocal dilution factor including minimum required dilution) will be reported.

ADAb status at sample level:

An ADAb status of positive (ADAb+) will be concluded for any sample with an ADAb level that is Positive Screen (PS) and Positive Immunodepletion (PI);

An ADAb status of negative (ADAb-) will be concluded for any sample with an ADAb level that is either Negative Screen (NS) or Positive Screen (PS) and Negative Immunodepletion (NI);

Participant Classification:

A participant will be classified as having ADAb positivity at Baseline if the Day 0, predose result is ADAb+

A participant will be classified as overall positive if at least one post-Baseline measurement is ADAb+ (see definition above) (this includes participant who have negative and positive results at baseline)

A participant will be classified as overall negative if at all post-Baseline visits the ADAb status is negative (this includes study participants who have positive and negative results at Baseline)

A participant will be classified as having treatment-emergent ADAb positivity when meeting one of the following criteria:

- The Baseline result is ADAb-, and at least one postBaseline time point is ADAb+
- The Baseline result is ADAb+, and at least one postBaseline measurement shows a predefined fold increase in titer from the Baseline value (the fold increase from Baseline required to meet these criteria will be defined with the development of the assay and will be included in the TFLs)

Analysis:

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant. All analyses will be run on the SS, unless specified otherwise. For all tabulations, percentages will be calculated based on the number of study participants with non-missing data.

All individual study participant-level ADAb results will be listed for all study participants. This will include the screening assay, confirmatory assay, and titer (if applicable).

Number and percentage of study participants with a positive and negative ADAb status will be summarized at the time of each visit and overall.

In addition, the first occurrence of treatment-emergent ADAb positivity (based on the definitions above) will be summarized (number and percentage of study participants) at each postBaseline visit, based on the PK. This tabulation will present the number and percentage of study participants at each postBaseline visit who fulfill at least one of the above defined criteria for treatment-emergent positivity; study participants will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, study participants will be counted in the denominator (assuming a measurement is available). For all tabulations, percentages will be based on the number of observations at each visit. This summary will exclude any samples with CZP concentrations confirmed to be above the drug tolerance.

A listing will be presented showing the CZP concentrations and ADAb measurements in the same output in adjacent columns, based on the PK. The listing will include the CZP

concentration and ADAb status (positive or negative) and screening assay results (PS or NS) and confirmatory assay results if applicable (NI or PI), together with the titer if applicable. In addition, the time since the administration of study medication will be reported (in days). ADAb samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged.

Finally, individual participant plots will be presented displaying the ADAb titer and CZP concentrations overlaid on the same figure. The figure will also show the timing and dose of each administration of CZP received during the study. The ADAb data will be plotted using a semi-logarithmic scale. ADAb samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged on the plot.

The rules for handling values that are BLQ in the CZP concentration data are described in Section 5.5.1.1.1. For the ADAb data, any negative results for which there are no titers (as applicable) available at a specific visit will be substituted with 0.001 for the purpose of the figure.

**Has been changed to:**

ADAb antibodies will be measured using a tiered assay approach: screening assay, confirmatory assay and titration assay. **The ADA status at sample level will be defined in** Table 5–1 **.**

A screening cut point will be determined by the bioanalytical laboratory that will be used to determine the status of ADAb as Positive Screen (PS) or Negative Screen (NS). Samples presenting ADAb levels PS are considered "potentially ADAb positive" and will be further evaluated in the confirmatory assay, the result of which will be reported as either "Positive Immunodepletion" (PI) or "Negative Immunodepletion" (NI). Confirmed positive samples (reported as PI) will be titrated, and the titer (reciprocal dilution factor including minimum required dilution) will be reported.

ADAb status at sample level:

| **Table 8–1 : ADA status at Sample level** | |
|---|---|
| **ADA positive (ADAb+)** | **Sample values that are 'positive screen' and 'positive immuno-depletion'** |
| **ADA negative (ADAb-)** | **Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' if corresponding drug levels are equal or below the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADA or limit dictated by the ADA assay and project needs (e.g. 250 ng/ml).** |

| | |
|---|---|
| **ADA inconclusive** | **Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' but with corresponding drug levels above the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADA or limit dictated by the ADA assay and project needs (e.g. 250 ng/ml)** |
| **Missing** | **Samples that were not collected per schedule or that could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc.** |

Participant Classification:

A participant will be classified as overall positive if at least one post Baseline measurement is ADAb+ (see definition above) (this includes participant who have negative and positive results at baseline)

A participant will be classified as overall negative if at all post Baseline visits the ADAb status is negative (this includes study participants who have positive and negative results at Baseline)

A participant will be classified as having **classification** of **ADA status as stated** in **below Table 5–2 .**

**Table 8–2 : Classification of ADA status**

| | | |
|---|---|---|
| **1.** | **Pre ADA negative and treatment-emergent ADA negative** | **Study participants who were negative at Baseline and negative at all sampling points post treatment till time point of interest** |
| **2.** | **Pre ADA negative and treatment-(emergent) induced ADA positive** | **Study participants who were negative at Baseline and positive at any sampling point post treatment. This group also included study participants who had a missing pre-treatment sample (either missing or insufficient volume) with 1 or more positive post-treatment samples.** |
| **3.** | **Pre ADA positive and treatment-emergent reduced ADA** | **Study participants who were positive at Baseline, and negative at all sampling points post treatment till time point of interest** |
| **4.** | **Pre ADA positive and treatment-emergent unaffected ADA positive** | **Study participants who were positive at Baseline and were positive at any sampling point post treatment with titer values of the same magnitude as Baseline (i.e., less than a predefined fold difference from the Baseline value of 4.11).** |
| **5.** | **Pre ADA positive and treatment-emergent ADA boosted positive** | **Study participants who were positive at Baseline and were positive at any sampling point post treatment with increased titer values compared to Baseline (greater than a predefined fold difference increase of 4.11 from Baseline value which is defined within the validation of the assay).** |

| | | |
|---|---|---|
| **6.** | **ADA inconclusive** | **Study participant for who the ADA participant status cannot be defined due to missing or inconclusive samples (this will include study participants from the SS for whom no ADA samples were collected).**<br>**Inconclusive [1]: Study participant that had negative ADA status at Baseline and post-Baseline samples missing per schedule or inconclusive, while others post-Baseline samples are ADA negative up to the time point of interest.**<br>**Inconclusive [2]: Participants who do not satisfy any of the above criteria** |
| **7.** | **Treatment emergent ADA positive** | **Combination of 2 and 5** |
| **8.** | **Pre-treatment ADA positive** | **Combination of 3, 4 and 5** |



Analysis:

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant. All analyses will be run on the SS, unless specified otherwise. For all tabulations, percentages will be calculated based on the number of study participants with non-missing data.

**Individual participant concentration-time profiles of CZP will be displayed graphically in linear and semi-logarithmic scale and grouped by MTX use at screening .**

All individual study participant-level ADAb results will be listed for all study participants. This will include the screening assay, confirmatory assay, and titer (if applicable).

**Summary table displaying the** number and percentage of study participants **with a positive ADA, negative ADA, inconclusive or missing ADA sample status at the time of each visit by treatment group. [Note that in case of presence of pre-ADA, no differentiation can be made between pre-ADA and treatment emergent ADA (either newly induced or boosted ADA). Note this table is not be used for incidence interpretation].**

**Based on the overall ADA study participant classification above from Table 10, the following will be determined and presented: summary tables displaying** the number and percentage of study participants **in each of ADA participant status categories (1–8), with the denominator being the total number of study participants having an individual ADA participant category defined during the corresponding analysis period and treatment group.** (**All** study participants will be **assigned to a category in this table and should not be confused with ADA incidence that is defined below).**

**Incidence and prevalence:**

- **Total prevalence of pre-Ab overall and by treatment group. Total prevalence of pre-Ab: n/NN % number of** participants **that have a pre-ADA positive ADA sample status,**

**with NN** being the denominator **defined as all participants having an evaluable baseline ADA sample**.

**Overall ADA incidence and by treatment group, Treatment-Emergent Anti-CZP Antibody Positivity Activity for combined results of treatment-boosted ADA-positive participants and treatment induced ADA-positive participants. n/N % of participants that are treatment emergent, with N being the denominator defined as all participants except the participants categorized as inconclusive.**

**Number and percentage of study participant Baseline Anti-CZP status and Treatment-Emergent Anti-CZP Antibody Status will be summarized during the entire study. The change in category from Baseline ADAb status including ADAb-, ADAb+, Missing and total will be presented in shift tables at each post-Baseline treatment treatment-emergent anti-CZP antibody status.**
**Treatment Treatment-Emergent Anti-CZP Antibody Status will be categorized as below:**

- **Negative : Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb-**
- **Positive <512 : Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb+ and ADAb titer is less than 512.**
- **Positive 512-<=1024: Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb+ and ADAb titer is greater than 512 and less and equal 1024.**
- **Positive>1024: Treatment Treatment-Emergent Anti-CZP Antibody Status is ADAb+ and ADAb titer is greater than 1024.**
- **Any positive : Study participants having treatment-emergent ADAb+.**
- **Total : total Treatment Treatment-Emergent Anti-CZP Antibody Status**

**Number and percentage of study participant Anti-CZP titer by visit will be summarized during the entire study. ADAb titer will be categorized as below:**

- **Negative : The ADAb status is ADAb-**
- **<=32 : The ADAb titer result is less than or equal to 32.**
- **>32-128: The ADAb titer result is greater than 32 and less than or equal to 128.**
- **>128-512: The ADAb titer result is greater than 128 and less than or equal to 512.**
- **>512-1024: The ADAb titer result is greater than 512 and less than or equal to 1024.**
- **>1024-4096: The ADAb titer result is greater than 1024 and less than or equal to 4096.**
- **>4096: The ADAb titer result is greater than 4096.**

A listing will be presented showing the CZP concentrations and ADAb measurements in the same output in adjacent columns, based on the SS. The listing will include the CZP concentration and ADAb status (positive or negative) and screening assay results (PS or NS) and confirmatory assay results if applicable (NI or PI), together with the titer if applicable. In addition, the time since the administration of study medication will be reported (in days). ADAb

samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged.

**Time course plots of all individual CZP plasma concentrations profiles (each participant corresponding to a line) (spaghetti plot) with identification of the individual ADA participant category using different colors ( categories 1, 3,4 and 7. If not sufficient participants in category 3 and 4, these could be combined for this plot). These plots will be produced on a linear and semilogarithmic scale and multi-panel per treatment group. Individual samples with positive ADA sample status will be visualized using a symbol or a red dot. Dosing nominal time points should be indicated below the x-axis. A similar plot may be considered for PD endpoints. The plot may be stratified based on MTX use at baseline/screening.**

**Change #9**

**Section 6.1.2 Protocol deviations**

A by-participant listing of important protocol deviations will be provided using the ASP.

**Has been changed to:**

A by-participant listing of important protocol deviations will be provided using the SS.

**A by-site participant listing of COVID-19 related important protocol deviations will be provided using the SS.**

**Change #10**

**Section 6.1.4 History of Rheumatoid Arthritis**

- Duration of RA (years) will be calculated as:
  - $Disease\ Duration = \frac{(Date\ of\ \text{screening} - Date\ of\ \text{diagnosis}\ of\ \text{RA})}{365.25}$

**Has been changed to:**

- Duration of RA (years) will be calculated as:
  - **Duration or RA (first persistent symptoms)= (screening date - first persistent symptoms)/365.25**
  - **Duration of RA (since date of diagnosis)=(screening date - date of** IMP Administration **diagnosis)/365.25.**

**Change #11**

**Section 6.1.7 AEs of Special Interest (AESIs)**

**Table 8–1:Adverse Events of Special Interest (AESIs)**

| AESIs term and other AE subsets | Extraction way | Term of SMQ (for SMQ extraction only) or other search strategy |
|---|---|---|
| AESIs: Infections, including serious opportunistic infections and tuberculosis | 1) Serious infections | |
| | 2) Opportunistic infections including tuberculosis, manual | 2) UCB defined search criteria for opportunistic infections including Tuberculosis |
| AESIs: Malignancies, including lymphoma | 1) SMQ<br>2) SMQ | 1) SMQ=”Malignant or unspecified tumours”<br>2) SMQ=”Malignant tumours”<br>Note: Non melanomic skin cancer will also be summarized by using HLT= “Skin neoplasms malignant and unspecified (excluding melanoma)” |
| AESIs: Congestive heart failure | 1) Congestive heart failure, manual | |
| | 2) Major adverse cardiovascular events (MACE) | 2) UCB defined search criteria[1)] |
| AESIs: Demyelinating-like disorders | Manual | Medical review of TEAE table |

| AESIs term and other AE subsets | Extraction way | Term of SMQ (for SMQ extraction only) or other search strategy |
|---|---|---|
| AESIs: Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia | SMQ | SMQ=”Haematopoietic cytopenias” on subset of serious TEAEs |
| AESIs: Serious bleeding events | SMQ | SMQ=”Haemorrhages” on subset of serious TEAEs |
| AESIs: Lupus and lupus-like syndrome | Manual | Medical review of TEAE table |
| AESIs: Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme) | Manual | Medical review of serious TEAE table |

1) Will include fatal and serious non-fatal myocardial infarctions, cerebrovascular events and congestive heart failures based on MedDRA terms and medical reviews.

**Has been changed to:**

**Table 8–1:Adverse Events of Special Interest (AESIs)**

| AESIs term and other AE subsets | Extraction way | Term of SMQ (for SMQ extraction only) or other search strategy |
|---|---|---|
| AESIs: Infections, including serious opportunistic infections and tuberculosis | 1) Serious infections | |
| | 2) Opportunistic infections including tuberculosis, manual | 2) UCB defined search criteria for opportunistic infections including Tuberculosis |
| AESIs: Malignancies, including lymphoma | 1) SMQ<br>2) SMQ | 1) SMQ=”Malignant or unspecified tumours”<br>2) SMQ=”Malignant tumours”<br>Note: Non melanomic skin cancer will also be summarized by using HLT= “Skin neoplasms malignant and unspecified (excluding melanoma)” |
| AESIs: Congestive heart failure | 1) Congestive heart failure, manual | |
| | 2) Major adverse cardiovascular events (MACE) | 2) UCB defined search criteria[1)] |
| AESIs: Demyelinating-like disorders | **SMQ** | **SMQ = “Demyelination (SMQ)”** |

| AESIs term and other AE subsets | Extraction way | Term of SMQ (for SMQ extraction only) or other search strategy |
|---|---|---|
| AESIs: Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia | SMQ | SMQ=”Haematopoietic cytopenias” on subset of serious TEAEs |
| AESIs: Serious bleeding events | SMQ | SMQ=”Haemorrhages” on subset of serious TEAEs |
| AESIs: Lupus and lupus-like syndrome | Manual | Medical review of TEAE table |
| AESIs: Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme) | Manual | Medical review of serious TEAE table |

1) Will include fatal and serious non-fatal myocardial infarctions, cerebrovascular events and congestive heart failures based on MedDRA terms and medical reviews.

# Approval Signatures

**Name:** RA0138-sap-amend

**Version:** 1.0

**Document Number:** CLIN-000203063

**Title:** RA0138-sap-amend_30AUG2022

**Approved Date:** 30 Aug 2022

| Document Approvals | |
|---|---|
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Qualified Person<br>Date of Signature: 30-Aug-2022 13:39:13 GMT+0000 |
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 30-Aug-2022 13:41:19 GMT+0000 |