STATISTICAL ANALYSIS PLAN

Study: UP0085

Product: CERTOLIZUMAB PEGOL

A POSTMARKETING, MULTICENTER, LONGITUDINAL, PROSPECTIVE, PHARMACOKINETIC, PHASE 1B STUDY IN PREGNANT WOMEN WITH CHRONIC INFLAMMATORY DISEASES TREATED WITH CIMZIA® (CERTOLIZUMAB PEGOL)

SAP/Amendment Number	Date
Final SAP	06 DEC 2019
SAP Amendment 1	15 DEC 2021
SAP Amendment 2	22 JUN 2023

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LIST OF ABBREVIATIONS

ADA	anti-CZP antibody
AE	adverse event
ASPS	All Study Participants Set
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CSR	Clinical Study Report
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
CV	coefficient of variation
CZP	certolizumab pegol
DAP	Data Analysis Plan
DEM	Data Evaluation Meeting
eCRF	electronic Case Report Form
ES	Enrolled Set
FDA	Food and Drug Administration
HLT	Higher Level Term
ICC	Intraclass Correlation Coefficient
ICF	informed consent form
ICH	International Council for Harmonization
IVF	in vitro fertilization
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
MSR	minimum significant ratio
OI	opportunistic infections
PD	Pharmacodynamics
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	standard deviation
SFU	Safety Follow-up

SMQ	standardized MedDRA query
SOC	system organ class
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TFLs	Tables, Listings and Figures

1 INTRODUCTION

This statistical analysis plan (SAP) provides the necessary information to perform the final statistical analysis for study UP0085. It also defines the summary tables, figures and listings (TFLs) to be generated for the final clinical study report.

The SAP is based on the final Protocol Amendment 2 (30 AUG 2022). All references to study protocol hereafter refer to this version of the protocol, and, unless otherwise specified, the study will be analyzed as described in this version of the protocol. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, or if analysis definitions must be modified or updated, this SAP will be amended accordingly.

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance documents (Phillips et al, 2003).

The study assesses any changes in certolizumab pegol (CZP) plasma concentrations over the course of pregnancy, relative to the postpartum period. CZP is approved in adults for the treatment of chronic inflammatory diseases. It is valuable to evaluate whether the physiologic changes underlying pregnancy impact the pharmacokinetic (PK) profile of CZP during pregnancy in order to ensure that women who require CZP treatment during pregnancy are able to achieve therapeutic steady state levels of CZP.

Revision(s) of this SAP will not be required for any subsequent amendments to the protocol which do not change the analyses described in this SAP.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

To assess systemic CZP exposure across the course of pregnancy in study participants with chronic inflammatory diseases

2.1.2 Secondary objectives

- To assess the formation of anti-CZP antibodies (ADA) across the course of pregnancy
- To assess the safety of CZP in study participants with chronic inflammatory diseases across the course of pregnancy

2.1.3 Other objectives

- To assess changes in body mass index (BMI), C-reactive protein (CRP) and albumin across the course of pregnancy

2.2 Study variables

2.2.1 Primary Outcome variable

Predose and postdose plasma CZP concentrations in women during pregnancy, relative to postpartum

2.2.1.1 Secondary Outcome variables

- Plasma levels of ADA throughout the study period
- Treatment-emergent adverse events from time of informed consent through Safety Follow-up (SFU)
- Pregnancy outcome

2.2.1.2 Other Outcome variables

- BMI
- CRP levels
- Albumin levels

2.3 Study design and conduct

This is a Phase 1B, multicenter, longitudinal, interventional, prospective, PK, open-label study evaluating the impact of pregnancy on the PK of CZP. The study will recruit women who are already on prescribed commercial CZP with both a dosing regimen selected with guidance from the participant's treating physician and an indication approved for use in their country, and who become pregnant and continue treatment with CZP. A postpartum predose blood sample taken 12 weeks (±1 week) after delivery, once the mother is considered to have returned to a pre-pregnancy physiological state, will serve as a within-participant reference sample. If possible, a postdose sample will be taken 1 week (±1 day) after the 12-week postpartum dose.

This study is considered interventional due to the collection of blood samples from the women, which is not part of routine clinical practice. However, it is noninterventional regarding treatment with CZP and will only include pregnant women who decided with their treating physician to continue treatment with CZP prior to being recruited for and enrolled in the study.

The study consists of a Screening Period, Sampling Period (consisting of a Pregnancy Period and Postpartum Period), and SFU contact, as shown in Figure 1-1 and described below.

The full Schedule of Activities is provided in the protocol (Table 1-1).

- **Screening Period:**

  Women of childbearing potential already on commercial CZP can register to indicate interest in the current study. After confirmation of pregnancy, the women will consent to participate in the study and will be eligible to enroll once CZP levels have reached steady state. Confirmation of steady state is based on participant records and/or reports from the prescribing physician indicating that the participant has taken CZP for at least 12 weeks at the same dosing regimen prior to the Enrollment Visit, which must take place at ≤10 weeks gestational age.

- **Sampling Period:**

  - **Pregnancy Period:**

    PK samples will be collected prior to the subsequent dose (predose) every 4 weeks (Q4W) starting with the first dose after enrollment. Further, postdose (7 ± 1 day after dose administration) PK samples will be collected every 8 weeks (Q8W) throughout the

pregnancy. It is expected that there will be approximately 6 predose and 3 postdose PK samples collected per study participant (if there are no discontinuations) over the pregnancy.

- **Postpartum Period:**

  A predose sample 12 weeks (±1 week) postpartum will be collected during the Postpartum Period. If possible, 1 additional postdose sample 1 week (±1 day) after the 12 weeks postpartum dose will also be collected.

- **Safety Follow-up contact:**

  All study participants will be contacted via telephone for a SFU 5 weeks (±5 days) after final study visit.

If any participant withdraws early, she will complete the SFU contact.

The end of the study is defined as the date of the SFU/last contact of the last participant in the study.

Number of participants:

Approximately 25 to 30 participants are planned to be screened to achieve approximately 20 enrolled study participants (i.e., study participants who have provided the first blood sample). Enrollment will occur until a minimum of 10 study participants have longitudinal data (defined as at least 4 quantifiable predose and 2 quantifiable postdose PK samples during pregnancy and at least 1 quantifiable postpartum sample) over the study period.

Treatment groups and duration:

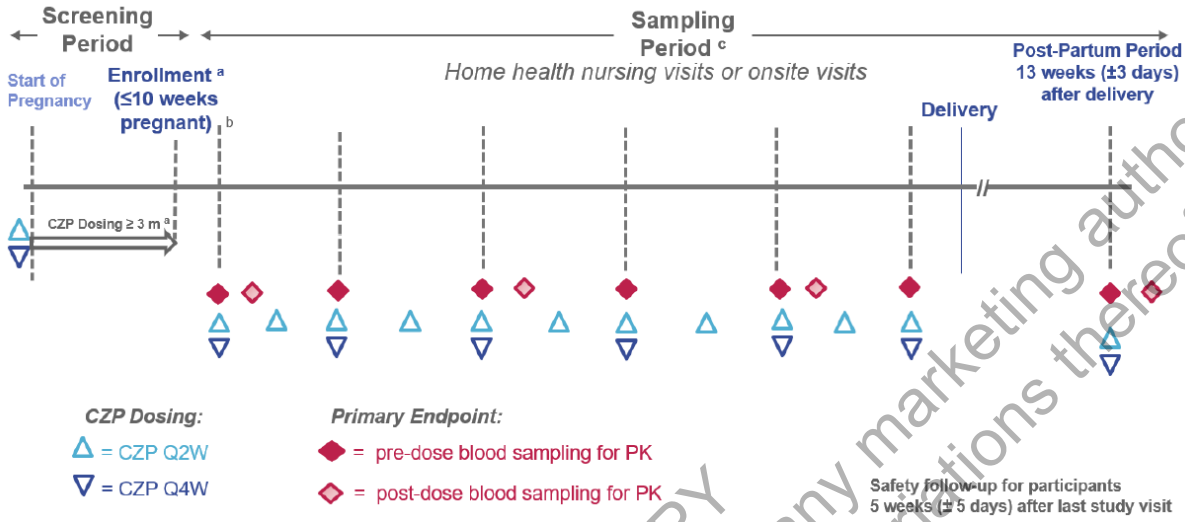
This study will include pregnant women who have decided to continue treatment with commercial CZP in accordance with their treating physician prior to participating in the study. Study participants will be responsible for obtaining and administering commercially available CZP under the care of their physician and according to the locally approved product label.

The total study duration for a study participant will be a maximum of 53 weeks (40 weeks gestation period and up to 13 weeks (±3 days) postpartum).

2.3.1 Schema

A schematic of the study design is provided in Figure 1-1.

Figure 1-1: Study Diagram



CZP=certolizumab pegol; PK=pharmacokinetics; Q2W=every 2 weeks; Q4W=every 4 weeks
[a] CZP dosing for at least 12 weeks before enrollment
[b] First CZP dose post-enrollment
[c] Timing and the number of visits across the pregnancy will vary for individual study participants

2.4 Determination of sample size

Because no formal hypothesis testing will be conducted, the sample size of 15 study participants is deemed sufficient for a small exploratory Phase 1B study. It is expected that up to 25 to 30 women will need to be screened to ensure that approximately 20 study participants are enrolled, in order to allow for approximately 15 evaluable study participants. These 15 evaluable participants are expected to provide the minimum of 10 study participants providing longitudinal data (defined as at least 4 quantifiable predose and 2 quantifiable postdose PK samples during pregnancy and at least 1 quantifiable postpartum sample) over the study period.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, study participant data listings, and statistical output will be performed using SAS® Version 9.3 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results.

For categorical parameters, the number and percentage of study participants in each category will be presented. Unless otherwise noted, the denominator for percentages will be based on the number of study participants included in the respective analysis set. Study participants with missing PK/ADA data will be addressed in Section 4.2.3. Other missing data can generally be accounted for using one of the following approaches:

- Percentages will be summarized based on all study participants in the analysis set and a "Missing" category (corresponding to study participants with missing data for the variable being summarized) will be included as the last row in the list of categories being summarized.
- Percentages will be based only on those study participants with observed data for the variable being summarized. As the denominator may be different from the number of study participants in the analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be "n/Nsub (%)", where n=number participants in a category and Nsub=total number of participants with observed data.

The approach to be considered will be further specified in the relevant section of the variable of interest.

Unless otherwise noted, all percentages will be displayed to one decimal place. No percentage will be displayed for zero counts, and no decimal place will be presented when the percentage is 100%.

Unless stated otherwise, continuous endpoints will be summarized by timepoints.

For continuous parameters, descriptive statistics will include number of study participants with available measurements (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum (unless otherwise stated). If n=3, only n, mean, median, minimum and maximum will be displayed. If n<3, only n, minimum and maximum will be displayed. For both cases, any summary statistics that are not displayed will be replaced with 'NA' and explained in a footnote.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer.
- Mean, SD, and median will use 1 additional decimal place compared to the original raw value from the Case Report Form (CRF).
- Coefficient of variance (CV [%]) will be presented with 1 decimal place.
- Minimum and maximum will have the same number of decimal places as the original raw value.

If the number of decimal places reported in the raw data is varied then either the maximum raw number of reported decimal places or 3 will be used, whichever is the lowest, as a guide for the descriptive statistics.

Unless stated otherwise, statistical tests will be performed 2-sided and p-values will be rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999." Statistical comparison will be performed at the 0.05 level of significance.

The SAS® outputs supportive of any statistical model (i.e., all excluding the descriptive analyses) will be provided as a separate PDF document in addition to TFLs. These outputs will be included in the 'Documentation of Statistical Methods' section of the clinical study report.

The abbreviation for certolizumab pegol is CZP and will be used in tables and listings headers. Unless otherwise specified, in the TFLs study participants on Certolizumab pegol will be displayed in columns by dosing regimen and all study participants as:

- "Not Dosed"
- "CZP 200mg Q2W"
- "CZP 400mg Q2W"
- "CZP 400mg Q4W"
- "All Dosed Participants"

An additional "Other" category will be added to the tables in case there are dosing regimens outside those listed. The "Not Dosed" category includes participants who enrolled but did not record a CZP dose relative to any PK samples prior to discontinuation. The "All Dosed Participants" category includes participants in CZP 200mg Q2W, CZP 400mg Q2W and CZP 400mg Q4W combined.

Study Participants will be grouped according to the commercial CZP dosing regimen that was in effect at enrollment (actual dose). Any participant with a dose reduction or increase will be summarized in the initial dosing regimen group.

All repeated and unscheduled measurements will be presented in the data listings, where applicable. The following general rules will apply to all repeated and unscheduled measurements:

- Unscheduled measurements will not be used in the descriptive statistics.
- For repeated measurements only the scheduled latest value can be used in the calculation of the descriptive statistics.

Unless otherwise stated, listings will be sorted by dosing regimen, study participant number, variable (if applicable) and visit (if applicable, including timing relative to dosing if applicable). All listings will include repeat and unscheduled measurements; such measurements will appear in chronological order together with the scheduled visits, i.e., a repeated measurement will appear directly after the visit and time relative to dosing for which the repeat measurement was performed. In all the listings dates will be presented in the format 'YYYY-MM-DD' and times will be presented in 24h clock format as 'hh:mm'.

3.1.1 Summary statistics specific to PK data

For CZP Plasma concentrations, geometric mean, geometric coefficient of variation (geometric CV (%)), 95% CI for the geometric mean (assuming log-normally distributed data) will only be calculated if at least ⅔ of the values of interest are above the LLOQ (0.032 ug/mL). If this is not the case, only median, minimum and maximum will be presented.

The 95% CI for the geometric mean will be calculated by obtaining the lower and upper 95% CI for the arithmetic mean on the log-transformed data and back-transforming to obtain the respective values for the geometric CI.

The geometric CV (%) will be calculated using the following formula:

$$CV = \sqrt{e^{SD_{ln}^2} - 1}$$

where SD_{ln} represents the standard deviation of the log-transformed plasma concentration values.

The intraclass correlation coefficient (ICC) will be calculated using the following formula:

$$\rho = \frac{\sigma_r^2}{\sigma_r^2 + \sigma_\epsilon^2}$$

Where σ_r^2 represents the variance of the random effect and σ_ϵ^2 represents the variance of the residual in the linear mixed effects model as described in Section 9.1.2.

3.1.2 Unit conversion for height, weight and BMI formula

Even if BMI is available in the database, BMI (in kg/m^2) will be recalculated during analysis based on height (in m) and weight (in kg) values collected in the database, and the calculated values will be used in the statistical analysis.

If height is recorded in inches, the height conversion is:

Height (m) = 0.0254*Height (inches)

If weight is recorded in pounds, the weight conversion is:

Weight (kg) = 0.45359237*Weight(lb)

The formula for BMI (kg/m^2) calculation is:

$$\text{BMI} = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$$

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day

The relative day will be included in some listings and will be calculated as described below. The way that relative day is calculated depends on when the given event occurs relative to the date of first day of enrolment into the study.

Relative day 1 is the date of first day of enrolment into the study.

- If the study participant is not discontinued from the study and the event start (stop) date occurred on or after the first day of enrolment into the study, but prior to the SFU visit date, relative day is calculated as start (stop) date of the event minus date of first day of enrolment into the study + 1.
- If the study participant is discontinued from the study and the event start (stop) date occurred on or after the first day of enrolment into the study, but prior to the stop date, relative day is calculated as start (stop) date of the event minus date of first day of enrolment into the study + 1.
- If the study participant completes the SFU visit and the event start (stop) date occurred after the SFU visit date, the relative day to the most recent CZP dose is calculated as start (stop) date of the event minus most recent CZP dose date. The relative day in this situation should be preceded by a '+'

- If the study participant does not complete the SFU visit and the event start (stop) date occurred after the study stop date, the relative day to the most recent CZP dose is calculated as start (stop) date of the event minus most recent CZP dose date. The relative day in this situation should be preceded by a '+'
- If the event start (stop) date occurred before the first day of enrolment into the study, the relative day is calculated as start (stop) date of the event minus first day of enrolment into the study. The relative day in this situation should be preceded by a '-'.

Relative day will only be computed for fully completed dates and will be left blank for partial dates.

3.2.2 Study periods

The study consists of a Screening Period, Sampling Period (consisting of a Pregnancy Period and Postpartum Period), and a Safety Follow-up (SFU) contact, as described below. Gestational week (i.e., week of gestational age) is determined from the time since the first day of the last menstrual period or, if the participant had undergone in vitro fertilization (IVF), from the date of birth and gestational age recorded for the pregnancy outcome and then back-calculated to get the gestational week for each PK sample.

- Screening Period: Starts at the confirmation of pregnancy at screening and ends at the start of the enrolment date (Participant having taken CZP for at least 12 weeks at the same dosing regimen prior to the Enrollment Visit, which must take place at ≤10 weeks gestational age).
- Sampling Period: The total study duration for a study participant will be a maximum of 53 weeks (40 weeks gestation period and up to 13 weeks (±3 days) postpartum).
  - Pregnancy Period: Starts at enrolment and ends on the day of delivery. Pregnancy may take the entire length of the gestation period (up to 40 weeks).
  - Postpartum Period: Starts the day after the date of delivery and ends after the final postpartum sample is taken.
  - Trimesters: Defined using the gestational week and distinguished as first (up to 12 weeks and 6 days' gestation), second (13–28 weeks and 6 days' gestation), and third (any time at or after 29 weeks' gestation)
- Safety Follow-up contact: The SFU visit will be defined for all study participants who complete the study, or for study participants who discontinue early including those who discontinue from CZP. For participants who complete the study, the SFU will be conducted 5 weeks (+/-5 days) after final study visit. For participants who discontinue, the SFU visit will still be completed.

In case that the SFU date is not available, the last contact date will be used as end of the SFU period. A participant is considered to have completed the study if she has completed all phases of the study per protocol including the final study contact (SFU).

The end of the study is defined as the date of the SFU/last contact of the last participant in the study.

3.3 Definition of Baseline values

For summaries of all participant demographic data, Baseline value for a study participant is defined as the latest measurement for that study participant up to and including the day of enrolment into the study, unless otherwise stated. If a Baseline assessment is taken on the same day as study enrolment, it is eligible to be used as the Baseline value, even in the case that the time of the assessment is recorded as taking place after the time of study enrolment. However, such cases should be rare as study center personnel are instructed to do all assessments at the Baseline visit prior to enrolment. If a Baseline measurement is missing or not collected, and a Screening value is available, the Screening value will be utilized as Baseline instead. If no measurement is available prior to study enrolment, then the Baseline value is treated as missing.

For summaries of CRP, Albumin, BMI and anti-CZP antibody data, the postpartum measurement will be used as the reference point based on the postpartum measurement collected at Visit 5. If there was no sample collected at Visit 5, then the last available postpartum sample will be used. If the postpartum measurement is missing or not collected (i.e., the postpartum value is not available), then the reference value is treated as missing.

For summaries of plasma concentration, the postpartum measurements will be used as the reference point instead of the day of enrolment based on both the predose and postdose postpartum PK samples. If either the predose or postdose postpartum PK measurement is missing or not collected, (i.e., the postpartum value is not available), then the respective reference value is treated as missing.

3.4 Protocol deviations

No protocol deviation is permitted, either in retrospect or prospect.

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the key safety or PK outcomes (if applicable) for an individual study participant. The criteria for identifying important protocol deviations will be defined within the important protocol deviations document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

3.5 Analysis sets

There will be 4 analysis sets for the study: the All Study Participants Set (ASPS), the Enrolled Set (ES), the Safety Set (SS) and the Pharmacokinetic Per Protocol Set (PK-PPS).

3.5.1 All Study Participants Set

This will be the largest analysis set, consisting of all study participants who have signed the Informed Consent Form (ICF) and will include all participants who pass screening as well as screen failures. For participants who fail screening and subsequently re-screen, only the successful screening record(s) will be included in the ASPS.

3.5.2 Enrolled Set

The ES will include all study participants who are confirmed as having signed the ICF to participate in the study and have provided the first blood sample. For participants who re-enroll

after discontinuation, both enrollments will be included, and tables and listings will provide the participant identifiers in a footnote.

3.5.3 Safety Set

The SS will include all enrolled study participants who are dosing with commercial CZP per protocol at Screening.

3.5.4 Pharmacokinetic Per Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the SS, consisting of those study participants for whom at least one predose or postdose sample is available which was not impacted by an important protocol deviation.

3.6 Treatment assignment and treatment groups

The study will include pregnant women who have decided to continue treatment with commercial CZP in accordance with their treating physician prior to participating in the study. The commercially approved dosing regimens (200mg Q2W or 400mg Q2W or 400mg Q4W) will be permitted following the guidance of each study participant's physician.

After enrolment into the study, the study participant's physician may modify the dosing regimen as necessary. In such cases, non-approved CZP dosing regimens will also be allowed, at the discretion of the study participant's physician and in a manner independent of this study, as long as the regimen does not exceed 400mg Q2W and the dose is recorded in the diary. All dosing regimens outside the commercially approved will be categorized as other.

3.7 Center pooling strategy

No center pooling is planned for this study.

3.8 Coding dictionaries

All medications other than CZP will be classified by WHO Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term, using version MAR/2021 or later of the World Health Organization Drug Dictionary (WHO-DD), according to UCB standard operating procedures. Medical procedures will not be coded.

All adverse events (AEs) will be considered as treatment emergent adverse events (TEAEs) and will be classified by primary system organ class (SOC), high level term (HLT) and preferred term (PT) using MedDRA® version 24.1 or later. UCB Standard Operating Procedures will be followed.

3.9 Changes from protocol-defined analyses

The following change from the protocol have been implemented in the SAP:

- The protocol stated the secondary outcome variable of 'adverse events from time of informed consent through Safety Follow-up', this will now be 'Treatment-emergent adverse events from time of informed consent through Safety Follow-up'.
- The protocol defines 'baseline' for plasma concentration data as the predose measurement 12 weeks (±1 week) postpartum. In the SAP, tables and figures, the name for the reference point was changed to 'postpartum'.

- Clarification was added to the Enrolled Set definition to include participants who re-enrolled. The SS definition was updated to include all participants with ongoing CZP dosing at screening. PK-PPS definition was clarified to include participants for whom at least one predose or postdose sample is available which was not impacted by an important protocol deviation.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The following covariates will be included in the primary analysis model specified in Section 9.1.2:

- disease phenotype
- gestational week
- trimester and
- dose point

The covariates will be defined as: disease phenotype (rheumatoid arthritis, psoriatic arthritis, psoriasis, Crohn's disease, axial spondyloarthritis and ankylosing spondylitis) a 6-category variable, gestational week (that is, at the time point when sample is collected) as a continuous variable, trimester (trimester 1, 2, 3, or postpartum) as a 4-category variable, and dose point (predose or postdose) as a binary variable. In case of overfitting, disease phenotype will be excluded from the model.

4.2 Handling of dropouts or missing data

There will be no special procedures for handling missing outcome data. Only the imputation of missing or partial dates for safety assessments, as well as handling values below the LLOQ in the PK data will be conducted.

4.2.1 Handling of missing data for AE

All AEs will be considered TEAEs in this study. For analyses of TEAEs, a complete date must be established to correctly identify the TEAE as occurring during the pregnancy period or not. For purposes of imputing missing components of partially reported start and stop dates for TEAEs, the algorithms listed below will be followed.

Although the algorithms for pregnancy period or not depend on the onset date, imputation rules are provided for stop date as well, as these may be needed for certain statistical analyses, such as an analysis of TEAE prevalence or TEAE duration.

Start and stop dates of TEAEs will be displayed as reported in the study participant data listings (i.e., no imputed values will be displayed in data listings).

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of study enrolment is not the same as the month and year of TEAE onset, then use the 1st of the month
- If only the month and year are specified and the month and year of study enrolment is the same as the month and year of TEAE onset, then use the date/time of study enrolment

- If only the year is specified, and the year of study enrolment is the same as the year of TEAE onset, then use the date/time of study enrolment
- If the TEAE onset date is completely unknown, then use the date of study enrolment

Imputation of 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 31st of that year
- If the imputed stop date is after last contact date, use last contact date.
- If the TEAE is resolved and the stop date is completely unknown, then do not impute the stop date

Other imputation

In addition, the following will apply for presenting TEAE in summary tables:

- if the intensity of an TEAE is unknown, it will be considered as severe.
- If the relationship to CZP is missing, it will be considered as related.

For seriousness, no imputation rule will be applied, the worst-case approach will be applied for the analysis of Serious TEAEs (i.e., the missing seriousness will be considered as serious if missing).

4.2.2 Handling of missing data for prior and concomitant medications

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days. In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the electronic case report form (eCRF).

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of study enrolment is not the same as the month and year of the start date, then use the 1st of the month
- If only the month and year are specified and the month and year of study enrolment is the same as the month and year of the start, then use the date of study enrolment
- If only the year is specified, and the year of study enrolment is not the same as the year of the start date, then use January 1 of the year of the start date
- If only the year is specified, and the year of study enrolment is the same as the year of the start date, then use the date of study enrolment
- If the start date is completely unknown, and the stop date is unknown or not prior to the date of first dose after enrollment, then use the date of study enrollment

Imputation of 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 that year
- If the imputed stop date is after last contact date, use last contact date.
- If the stop date is completely unknown, do not impute the stop date

4.2.3 Handling of values below the LLOQ in PK data

Unless otherwise stated, PK measured values below the limit of quantification (BLQ) will be reported as the values of LLOQ/2 (0.016 ug/mL) for the summary statistics and figures but as BLQ for listings. No imputation will be used for missing samples.

4.3 Interim analyses and data monitoring

No interim analyses or data monitoring is planned.

4.4 Multicenter studies

No exploration of treatment by center interaction will be investigated.

4.5 Multiple comparisons/multiplicity

No adjustments for multiplicity or multiple comparisons are planned.

5 STUDY POPULATION CHARACTERISTICS

5.1 Disposition of study participants

Study participant disposition will be summarized for the ASPS. In this summary, the dates of first study participant screened and date of last study participant last visit, number of screened study participants, and the number of study participants included in each analysis set (ES, SS, PK-PPS) will be presented for all participants and by dosing regimen overall and for each site.

The disposition of study participants into dosing regimen groups and analysis sets (ES, SS and PK-PPS) will also be summarized on the ES.

Reasons for screen failures (as collected on the Study Termination Screen Failure of the case report form (CRF) page) will be summarized for the ASPS who failed to be enrolled.

The number and percentage of study participants will be summarized using the ES. The primary reason for study discontinuation as collected on the Study Termination CRF page will be provided in this table.

Finally, the number of enrolled study participants who discontinued the study due to TEAEs will be summarized.

Study disposition and termination details will be listed for the ASPS. Additional listings on the ES will be created on study discontinuation, study participant analysis sets and visit dates. A listing will also be provided for study participants who did not meet the study eligibility criteria.

5.2 Protocol deviations

A summary displaying the number and percentage of study participants with an important protocol deviation will be provided on the ES, including a summary of study participants excluded from the PK-PPS due to important protocol deviations.

A by-study participant listing of important protocol deviations will be provided for all study participants in the ES.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

The following demographic variables measured at Baseline to be summarized for the ES are: age (years), country, race, height (cm), body weight (kg) and BMI (kg/m^2). Age and BMI will be summarized as continuous variables only. Gender, confirmation of pregnancy and ethnicity will only be listed.

By-study participant listings on demographics will be provided for the ASPS.

6.2 Other Baseline characteristics

Other baseline characteristics to be summarized are lifestyle characteristics based on SS.

Details of tuberculosis (TB) testing will not be summarized. TB testing will be performed if the study participant has not been tested within 6 months prior to Screening and has no associated clinical evidence of an active TB infection. However, this data is not captured in the electronic database and hence no summary table or listing will be produced.

6.3 Medical history and concomitant diseases

Previous medical history is defined as conditions that have resolved prior to study entry.

Ongoing medical history is defined as conditions that are ongoing at the time of study entry.

Previous and on-going medical history will be summarized together by MedDRA System Organ Class (SOC) and Preferred Term (PT), by dosing regimen and overall including the number and percentage of study participants with each condition. The table summaries will be ordered alphabetically for SOC and in terms of decreasing frequency for PT within SOC. In the event of ties, PT will be ordered alphabetically.

The summaries will be presented on the SS.

Medical history will be listed by dosing regimen and study participant including the reported term, PT, and SOC for the ES. A glossary of all medical history conditions will be presented including the reported term, PT and SOC.

Medical procedures and medical procedure history will be listed for all study participants on the ES.

6.4 Medical conditions leading to CZP use

Medical conditions identified as the primary condition for CZP use will be summarized using the number and percentage for the SS. Primary medical conditions for Cimzia use as well as other medical conditions reported on the electronic Case Report Form (eCRF) but not identified as primary will be included in a listing. The medical condition decodes (MHDECOD) for the listing include:

- Psoriatic arthropathy

- Psoriasis
- Rheumatoid arthritis
- Arthritis
- Ankylosing spondylitis
- Axial spondyloarthritis
- Spondylitis
- Crohn's disease
- Juvenile idiopathic arthritis

6.5 Prior and concomitant medications

Study participants are permitted to continue on their prescribed medical therapy for the disease in accordance with the instructions of their treating physician.

Any treatment other than commercial CZP (CZP dosing dates and times will be collected separately in a diary), including over-the-counter products and supplements, must be recorded in the study participant's notes (source documentation) and provided on the eCRF. This record should include the name of the drug, the dose, the route, and date(s) of administration, and the indication for use.

For the purposes of this study:

- Past medications are those that are ongoing at the time of the first day of the last menstrual period and those that started after the first day of the last menstrual period and stopped prior to entering the screening period. For participants with IVF, past medications are those that are ongoing 12 weeks prior to screening or started within 12 weeks prior to screening and stopped prior to entering the screening period.
- Prior medications are those that are ongoing at the time of the first day of the last menstrual period and those that started after the first day of the last menstrual period but prior to entering the screening period. For participants with IVF, prior medications are those that are ongoing 12 weeks prior to screening or started within 12 weeks prior to screening.
- Concomitant medications are medications with at least 1 day in common with the screening period or sampling periods.
- Prior medications may include both past medications and concomitant medications.

The number and percentage of study participants taking past, prior and concomitant medications will be summarized for the SS.

A by-study participant listing of all past, prior and concomitant medications will be provided on ES.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study participants will be provided with CZP outside the study; hence compliance will not be measured.

8 EFFICACY ANALYSES

Not applicable.

9 PHARMACOKINETIC AND IMMUNOGENICITY ANALYSES

9.1 Statistical analysis of the primary outcome variable

9.1.1 Derivations of primary outcome variable

The primary endpoint will be summarized and listed using the PK-PPS. Individual samples marked 'Excluded from analysis' according to the PD review log 'Action for analysis' column will be deselected from the primary analysis.

Predose and postdose plasma CZP concentrations in women during pregnancy, relative to postpartum, will be analyzed as measured. Data analysis may be conducted on log transformed data (and back-transformed results displayed) where necessary.

9.1.2 Primary analysis of the primary outcome variable

The CZP plasma concentrations (primary variable) will be analyzed using a linear mixed effects model with fixed effects for disease phenotype, gestational week, trimester [trimester 1, 2, 3, or postpartum] and whether the sample was predose or postdose [binary indicator], and the random effect will be study participant. Within this model trimesters will be defined as follows: trimester 1 (≤12 weeks and 6 days' gestation), trimester 2 (13–28 weeks and 6 days' gestation), trimester 3 (≥29 weeks' gestation) and postpartum.

A compound symmetry covariance structure will be used, as this was decided to be the most appropriate structure given the context of this data. In case of overfitting, disease phenotype will be excluded from the model.

Adjusted mean differences with 95% CI of CZP plasma concentrations between samples taken each pregnancy trimester and postpartum will be estimated within this linear mixed effects model using contrasts. These adjusted mean differences and 95% CIs will be displayed graphically in a forest plot.

ICC may be provided to describe the consistency of CZP absorption from the same participant based on the linear mixed effects model as described in Section 3.1.1.

Data analyses may be conducted on log-transformed data, based on visual inspection of the data. This will be based on visual inspection of histograms, boxplots and quantile-quantile plots for each dosing regimen which will be included as part of the statistical appendices. If the data show a departure from normality, data analysis will be conducted on log transformed data (and back-transformed results displayed).

9.1.3 Primary summaries of the primary outcome variable

The individual plasma concentrations of CZP (ug/mL) will be summarized over the course of pregnancy by dosing regimen and by trimester or dosing time point (predose or postdose) using graphs and descriptive statistics (number of observations [n], geometric mean, lower and upper 95% confidence intervals [CI], geometric CV, arithmetic mean, SD, median, minimum, and maximum values).

The graphs to be produced by dosing regimen include:

1. Individual CZP plasma concentration plots using gestational week with predose and postdose values plotted side by side,

2. Spaghetti plots of CZP plasma concentrations using gestational week with predose and postdose values plotted side by side, and
3. Geometric Mean plots by dosing regimen and sample time relative to dose, i.e., separately for predose and postdose. The time points will be based on trimester as defined in Section 3.2.2, including the postpartum period. The plot will show both a linear and semi-logarithmic scale side by side. The average predose (or postdose) results within trimester per participant will be used to calculate the geometric mean and 95% CI for all participants combined.

For the calculation of descriptive statistics, a plasma concentration below the lower limit of quantification (LLOQ) will be substituted by LLOQ/2. The geometric and arithmetic means and associated SD, lower and upper limits of 95% CI, and CV will be calculated only if at least two thirds of the individual data at a specific sampling point are measured, are above or equal to LLOQ, and n≥4. If n<4, a subset of summary statistics will be displayed as described in Section 3.1.

9.1.4 Exploratory analysis of the primary outcome variable

The linear mixed effects model from the primary analysis will also be fitted to the predose and postdose CZP plasma concentrations separately. Adjusted means and 95% CI for each model will be included in the forest plot.

CZP plasma concentrations will additionally be analyzed adjusting for CRP, albumin and BMI. These analyses will be conducted using the same linear mixed effects model used for the primary analysis with CRP, albumin and BMI as a covariate in 3 separate models. Results from these models should be interpreted with caution, due to the small sample size and relatively large number of covariates. Summary tables showing the mean differences and 95% CIs of each trimester vs post-partum estimated from the model contrasts will be presented.

9.2 Immunogenicity

All immunogenicity analyses will be performed using the SS.

9.2.1 Anti-drug antibodies sample status category definitions

Anti-drug antibodies (ADA) will be measured using a three-tiered assay approach: screening, confirmatory and titration assay.

Samples will first be evaluated in the screening assay (reported as 'negative screen' or 'positive screen'), followed by analysis of screened positive samples in the confirmatory assay to confirm the true positivity of the samples (reported as 'negative immuno-depletion' or 'positive immuno-depletion'). Samples that are confirmed as positive in the confirmatory assay will be evaluated in a titration assay to quantify the ADA level and will be reported as titer (reciprocal dilution factor including minimum required dilution [MRD]).

The ADA sample status will be determined for each visit where samples were collected for ADA analysis (both scheduled and any unscheduled visits).

- Sample values that are either 'negative screen' or the combination of 'positive screen' and 'negative immunodepletion' will be defined as **ADA negative** if corresponding CZP concentrations are equal or below the validated drug tolerance limit of the ADA assay (100 ug/mL CZP) allowing detection of 100ng/mL ADA.

- Sample values that are either 'negative screen' or the combination of 'positive screen' and 'negative immunodepletion' but with corresponding CZP concentrations above the validated drug tolerance limit of the ADA assay will be defined as **ADA inconclusive**.
- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as **ADA positive**.
- Samples that could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc., will be defined as **Missing**.

9.2.2 Anti-drug antibodies participant titer classification

Once determined positive, a study participant's highest titer will be used to categorize ("titer classification") the study participant as follows:

- Positive ≤32
- Positive >32 - ≤128
- Positive >128 - ≤512
- Positive >512 - ≤1024
- Positive >1024 - ≤4096
- Positive >4096

9.2.3 ADA titer and classification summaries and analyses

The fold difference increase from postpartum value, i.e., the minimum significant ratio (MSR) determined during assay validation, will be reported in the relevant tables, listings and figures. It reflects the fold difference in titer level that is considered higher than the assay variation in titer determination.
The following summaries, figures and listings will be produced using the MSR and will be presented using the SS:

- 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 dosing regimen.
- Spaghetti plots of the individual time course plots of ADA titer (y-axis) by time (x-axis) for participants with at least one ADA positive sample status, with one line representing one study participant. Separate plots will be presented for each dosing regimen. Plots may be presented using a semi-logarithmic scale for the ADA titers (ADA negative samples will therefore be excluded from the plot). Time will be presented using gestational week.
- Summary statistics of ADA titers (mean, min, max, geomean) per time point and dosing regimen.
- Summary of titer classification for all study participants who test positive at any visit will be presented by category.
- The ADA results will be listed including the results from the screening assay, confirmatory assay, and titration assay (titer level), the ADA sample status, the drug concentration with indication if the drug level exceeds the ADA assay tolerance for detecting 100 ng/ml ADA or alternative level as defined above (Y/N).

In addition, the following figures will be produced to illustrate the impact of ADA on PK:

- Spaghetti plots of the individual CZP plasma concentrations (each participant corresponding to a line) over time will be produced on a linear and semi-logarithmic scale according to ADA titer classification. Gestational week should be indicated below the x-axis.
- Time course plots of individual CZP plasma concentrations (one plot per participant) superimposed with the participant's corresponding ADA titer over the course of the study will be presented. Plots may be presented using a semi-logarithmic scale for the ADA titers (ADA negative samples will therefore be excluded from the plot). Time will be presented using gestational week.

10 ANALYSIS OF OTHER OUTCOME VARIABLES

10.1 Other outcome variables

The other outcome variables to be presented are:

- CRP levels
- Albumin levels
- BMI

All three parameters will be listed on the SS only and will be used for the exploratory CZP model.

11 SAFETY ANALYSES

All safety analyses will be performed using the SS.

11.1 Pregnancy outcome

Pregnancy outcome by study participant will be included in a listing.

11.2 Infant illnesses

Illnesses reported for each infant by study participant will be included in a listing.

11.3 Adverse events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v24.1 or later version) and characterized as treatment emergent.

The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class and preferred term. The TEAEs will also be summarized by intensity and by relationship to CZP. TEAEs leading to discontinuation and serious TEAEs will also be summarized.

The following TEAE tables will be produced:

- Incidence of TEAEs Overview
- Incidence of TEAEs by SOC, HLT and PT
- Serious TEAEs
- Non-serious TEAEs
- TEAEs leading to death

- TEAEs leading to hospitalization or death
- TEAEs leading to study discontinuation
- Incidence of TEAEs by Maximum Severity
- Incidence of TEAEs by Maximum relationship
- Incidence of TEAEs by Trimester

The following TEAE of interest will be summarized in stand-alone tables:

- Serious infections including opportunistic infections (see Section 11.3.1)
- Malignancies or unspecified tumours including lymphoma
- Malignant Tumours
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events

For the following AEs of interest, no additional tables will be provided, as these are included in the standard AE summaries:

- Congestive heart failure
- Lupus and lupus-like syndrome
- Serious skin reactions (e.g., Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme).

Separate tables will be created to summarize each of the above TEAEs of interest by system organ class, high level term, and PT, where the TEAEs of interest are identified using standardized MedDRA queries (SMQ). An additional review cycle to confirm the targeted events will be implemented for opportunistic infections as described in Section 11.3.1.

All TEAEs and serious TEAEs will be listed using the SS. Details of serious TEAEs, TEAEs leading to death or study discontinuation will be listed. For results disclosure on public registries (e.g., ClinicalTrials.gov), TEAEs and serious TEAEs will be published.

11.3.1 Identification of opportunistic infections

A summary of opportunistic infections (including tuberculosis) will include all TEAEs identified using UCB-defined search criteria.

Identification Process

The steps below outline 2 ways (both programmatically and after manual review) in which opportunistic infections (or potential opportunistic infections) can be identified using standardized MedDRA queries (SMQ):

Step 1 [programmatic identification]: All TEAEs from 'Opportunistic infections (SMQ)' with a narrow scope are considered as automatically identified opportunistic infection, regardless of seriousness.

Step 2 [manual identification]: All other TEAE in the 'Opportunistic infections (SMQ)' with a broad scope will be evaluated on a case-by-case basis by the study physician to determine whether it is a true opportunistic infection (OI) of interest or not.

Review Process

A final listing for opportunistic infections (in the format described below) will be produced and reviewed by the study physician prior to finalizing the database.

The study programming team will produce an Excel listing of all AEs from the ADaM domain for participants with at least 1 TEAE falling within the broad scope of the 'Opportunistic infections (SMQ)' allowing a review of all the participants' AEs to establish OI of interest. The Excel listing will contain the following columns (using the descriptions below as the column headings in the Excel listing):

- Study ID
- Unique Participant ID
- AE Term (Verbatim)
- AE Preferred Term
- AE System Organ Class
- AE High Level Term
- AE Low Level Term
- Date of Onset
- Outcome of Adverse Event
- Date of Outcome
- TEAE Flag
- Serious Adverse Event?
- Relationship to Study Medication
- Intensity
- Action Taken with IMP
- Opportunistic Infection – Automatic; code and scope (Y/N)
- Opportunistic Infection – Manual Review; code and scope (Y/N)
- Flag for previously reviewed? (NEW/OLD)
- Data Cut Date
- Opportunistic Infection – Final Adjudication (Y/N)

Note the following about the final 5 variables in this listing:

- *Opportunistic Infection – Automatic*: This is flagged as "Y" if the criteria for automatic selection as described in "Step 1" of the identification process are met.

- *Opportunistic Infection – Manual Review*: This is flagged as "Y" if the criteria for case-by-case selection as described in "Step 2" of the identification process are met.
- *Flag* – This has a value of either "NEW" or "OLD". It is marked as "NEW" if the event is appearing for the first time in that run of the listing. Otherwise, if it has appeared previously, it is marked as "OLD". Unique records are determined by USUBJID AESPID for purposes of identifying whether an event has been modified from a previous run.
- *Date* – Only for cases where Flag is "NEW", this field will be populated with the data cut date for that particular run of the listing.
- *Opportunistic Infection – Final Adjudication* – For new events, this is always left blank by the programmers. It will be completed by the study physician for every event that appears in the listing. For events adjudicated as opportunistic, the field will be populated with a "Y".

Following the review by the study physician, the *Opportunistic Infection – Final Adjudication* column will be completed (as described above), and the spreadsheet will be returned to the study programming team via e-mail. The decisions documented in the returned file will be merged with AE data for final reporting in a summary table and flagged in the All Adverse Events listing.

11.4 Clinical laboratory evaluations

Clinical laboratory evaluations will not be conducted. CRP and albumin will be assessed as described in Section 10.1.

11.5 Vital signs, physical findings, and other observations related to safety

11.5.1 Vital signs

Measured values of vital signs will be summarized descriptively and reported using the SS.

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (°C)
- Respiratory Rate (breaths per min)

If any vital signs are repeated then the last or latest dated assessment will be used for tabulation purposes.

All vital signs will be summarized by dosing regimen and listed using the SS.

11.5.2 Physical Findings

Physical examination abnormalities will be listed using the SS.

12 REFERENCES

Phillips A, Haudiquet V. ICH E9 guideline 'Statistical principles for clinical trials: a case study'. Stat Med. 2003;22(1):1-11; discussion 13-7.

13 APPENDICES

13.1 AMENDMENT 1

Rationale for the amendment

The major purpose of this SAP amendment was to implement changes to align with more recent standards and make further clarifications for programming.

The main SAP amendments can be summarized as follows:

- Change of WHO Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term version to MAR/2021
- Change to MedDRA 24.1.
- Updates to prior and concomitant medication definitions
- Update to partial dates imputation
- Exclusion of selected TEAE tables from analysis

13.1.1 Coding Dictionaries (Section 3.8)

- Dictionary versions updated

13.1.2 Handling of partial missing dates for AEs (Section 4.2)

- If the imputed stop date is after last contact date, use last contact date.

13.1.3 Exclusion of TB summary from baseline analyses (Section 6.2)

Paragraph updated to:

Other baseline characteristics to be summarized are lifestyle characteristics. Details of tuberculosis (TB) testing will not be summarized. TB testing will be performed if the study participant has not been tested within 6 months prior to Screening and has no associated clinical evidence of an active TB infection. However, these data are not captured in the electronic database and hence no summary table or listing will be produced.

13.1.4 Definition of past and prior medications (Section 6.5)

- Past medications are those that are ongoing at the time of first day of the last menstrual period and those that started after the first day of the last menstrual period and stopped prior to entering the screening period.
- Prior medications are those that are ongoing at the time of first day of the last menstrual period and those that started after the first day of the last menstrual period prior to entering the screening period.
- Concomitant medications are medications with at least 1 day in common with the screening period or sampling periods.
- Prior medications may include both past medications and concomitant medications.

13.1.5 Exclusion of TEAE tables (Section 11.3)

For the following AEs of interest, no additional tables will be provided, as these are included in the standard AE summaries:

- Congestive heart failure
- Lupus and lupus-like syndrome
- Serious skin reactions (e.g., Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme).

13.2 AMENDMENT 2

Rationale for the amendment

The major purpose of this SAP amendment was to align text with protocol amendment 2 and with more recent standards, and to make further clarifications for programming.

The main SAP amendments can be summarized as follows:

- Change of sample size text to reflect the minimum required number of participants
- Inclusion of a Not Dosed group for the participant who withdrew from the study prior to dosing during the pregnancy period and change from 'All Participants' to 'All Dosed Participants' to avoid counting this participant twice.
- Clarification of the calculation of geometric CI and ICC
- Clarification of the definition of gestational week
- Rewording of the reference point for plasma concentration
- Updated the definitions of the ES, SS and PK-PPS
- Handling of missing dates for imputation rules
- Addition of a section to describe the summary of medical conditions leading to CZP use along with dictionary terms to use for identifying the medical conditions.
- Clarification of which PK graphs will be produced
- Details of anti-drug antibody status and classification definitions and summaries
- Addition of a listing to display infant illnesses
- Cosmetic and grammatical corrections
- Addition of a section for the identification of opportunistic infections

13.2.1 Sample size (Section 2.3 and Section 2.4)

Section 2.3 text updated to:

Enrollment will occur until a minimum of 10 study participants have longitudinal data (defined as at least 4 quantifiable predose and 2 quantifiable postdose PK samples during pregnancy and at least 1 quantifiable postpartum sample) over the study period.

Section 2.5 text updated to:

These 15 evaluable participants are expected to provide the minimum of 10 study participants providing longitudinal data (defined as at least 4 quantifiable predose and 2 quantifiable postdose PK samples during pregnancy and at least 1 quantifiable postpartum sample) over the study period.

13.2.2 Handling of small samples in summary tables (Section 3.1)

A rule was added:

If n=3, only n, mean, median, minimum and maximum will be displayed. If n<3, only n, minimum and maximum will be displayed. For both cases, any summary statistics that are not displayed will be replaced with 'NA' and explained in a footnote.

13.2.3 Addition of Not Dosed column (Section 3.1)

Section 3.1 dosing regimen labels updated to:

- "Not Dosed"
- "CZP 200mg Q2W"
- "CZP 400mg Q2W"
- "CZP 400mg Q4W"
- "All Dosed Participants"

An additional "Other" category will be added to the tables in case there are dosing regimens outside those listed. The "Not Dosed" category includes participants who enrolled but did not record a CZP dose relative to any PK samples prior to discontinuation. The "All Dosed Participants" category includes participants in CZP 200mg Q2W, CZP 400mg Q2W and CZP 400mg Q4W combined.

Study Participants will be grouped according to the commercial CZP dosing regimen that was in effect at enrollment (actual dose). Any participant with a dose reduction or increase will be summarized in the initial dosing regimen group.

13.2.4 Summary statistics specific to PK model (Section 3.1.1)

Section 3.1.1 header and text updated to:

The 95% CI for the geometric mean will be calculated by obtaining the lower and upper 95% CI for the arithmetic mean on the log-transformed data and back-transforming to obtain the respective values for the geometric CI.

The intraclass correlation coefficient (ICC) will be calculated using the following formula:

$$\rho = \frac{\sigma_r^2}{\sigma_r^2 + \sigma_\epsilon^2}$$

Where σ_r^2 represents the variance of the random effect and σ_ϵ^2 represents the variance of the residual in the linear mixed effects model as described in Section 4.1.

13.2.5 Conversion formulas and BMI calculation (Section 3.1.2)

This formula was removed from Section 6.1 and added to Section 3.1.2 including conversion factors for height and weight:

Even if BMI is available in the database, BMI (in kg/m^2) will be recalculated during analysis based on height (in m) and weight (in kg) values collected in the database, and the calculated values will be used in the statistical analysis.

If height is recorded in inches, the height conversion is:

Height (m) = 0.0254*Height (inches)

If weight is recorded in pounds, the weight conversion is:

Weight (kg) = 0.45359237*Weight(lb)

The formula for BMI (kg/m^2) calculation is:

$$\text{BMI} = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$$

13.2.6 Definition of gestational week (Section 3.2.2)

Text updated to:

Gestational week (i.e., week of gestational age) is determined from the time since the first day of the last menstrual period or, if the participant had undergone in vitro fertilization (IVF), from the date of birth and gestational age recorded for the pregnancy outcome and then back-calculated to get the gestational week.

13.2.7 Definition of postpartum as the reference point for PK analyses (Section 3.3)

Text updated to:

For summaries of CRP, Albumin and anti-CZP antibody data, the postpartum measurement will be used as the reference point instead of the day of enrolment, based on the postpartum measurement collected at Visit 5. If there was no sample collected at Visit 5, then the last available postpartum sample will be used. If the postpartum measurement is missing or not collected (i.e., the postpartum value is not available), then the reference value is treated as missing.

For summaries of plasma concentration, the postpartum measurements will be used as the reference point instead of the day of enrolment, based on both the predose and postdose postpartum PK samples. If either the predose or postdose postpartum PK measurement is missing or not collected, (i.e., the postpartum value is not available), then the respective reference value is treated as missing.

13.2.8 All Study Participants Set definition (Section 3.5.1)

The word 'Screened' was removed from the label and clarification on handling re-screened participants was added:

This will be the largest analysis set, consisting of all study participants who have signed the Informed Consent Form (ICF) and will include all participants who pass screening as well as screen failures. For participants who fail screening and subsequently re-screen, only the successful screening record(s) will be included in the ASPS.

13.2.9 Enrolled Set definition (Section 3.5.2)

Clarification was added to include participants who re-enrolled:

The ES will include all study participants who are confirmed as having signed the ICF to participate in the study and have provided the first blood sample. For participants who re-enroll after discontinuation, both enrollments will be included in the Enrolled Set. Tables and listings using the ES will list the participant identifiers in a footnote.

13.2.10 Safety Set definition (Section 3.5.3)

Clarification was added to include all enrolled participants:

The SS will include all enrolled study participants who are dosing with commercial CZP per protocol at Screening.

13.2.11 Pharmacokinetic Per Protocol Set definition (Section 3.5.4 and Section 9.1.1)

Section 3.5.4 text updated to:

The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the SS, consisting of those study participants for whom at least one predose or postdose sample is available which was not impacted by an important protocol deviation.

Section 9.1.1 text updated to:

The primary endpoint will be summarized and listed using the PK-PPS. Individual samples marked 'Excluded from analysis' according to the PD review log 'Action for analysis' column will be deselected from the primary analysis.

13.2.12 Additional changes from protocol-specified analyses (Section 3.9)

Two changes were added:

- The protocol defines 'baseline' for plasma concentration data as the predose measurement 12 weeks (±1 week) postpartum. In the SAP, tables and figures, the name for the reference point was changed to 'postpartum'.
- The Safety Set definition was modified to include all enrolled participants. These are participants who have been on a stable dose of commercial CZP per inclusion criteria regardless of whether the participant had the scheduled dosing administered during the Sampling Period according to Table 1-1 of the protocol.

13.2.13 Summary of Medical Condition Leading to CZP Use (Section 6.4)

Text updated to:

Medical conditions identified as the primary condition for CZP use will be summarized using the number and percentage for the SS. Primary medical conditions for Cimzia use as well as other medical conditions reported on the electronic Case Report Form (eCRF) but not identified as primary will be included in a listing. The medical condition decodes (MHDECOD) for the listing include:

- Psoriatic arthropathy
- Psoriasis
- Rheumatoid arthritis
- Arthritis
- Ankylosing spondylitis
- Axial spondyloarthritis
- Spondylitis
- Crohn's disease
- Juvenile idiopathic arthritis

13.2.14 Past and prior medications (Section 6.5)

The definitions of 'past' and 'prior' were clarified for participants with IVF:

- Past medications are those that are ongoing at the time of the first day of the last menstrual period and those that started after the first day of the last menstrual period and stopped prior to entering the screening period. For participants with IVF, past medications are those that are ongoing 12 weeks prior to screening or started within 12 weeks prior to screening and stopped prior to entering the screening period.
- Prior medications are those that are ongoing at the time of the first day of the last menstrual period and those that started after the first day of the last menstrual period but prior to entering the screening period. For participants with IVF, prior medications are those that are ongoing 12 weeks prior to screening or started within 12 weeks prior to screening.

13.2.15 PK random effects model description (Section 9.1.2)

Header updated to describe the model, and text updated to:

The CZP plasma concentrations (primary variable) will be analyzed using a linear mixed effects model with fixed effects for disease phenotype, gestational week, trimester [trimester 1, 2, 3, or postpartum] and whether the sample was predose or postdose [binary indicator], and the random effect will be study participant. Within this model trimesters will be defined as follows: trimester 1 (≤12 weeks and 6 days' gestation), trimester 2 (13–28 weeks and 6 days' gestation), trimester 3 (≥29 weeks' gestation) and postpartum.

A compound symmetry covariance structure will be used, as this was decided to be the most appropriate structure given the context of this data. In case of overfitting, disease phenotype will be excluded from the model.

Adjusted mean differences with 95% CI of CZP plasma concentrations between samples taken each pregnancy trimester and postpartum will be estimated within this linear mixed effects

model using contrasts. These adjusted mean differences and 95% CIs will be displayed graphically in a forest plot.

ICC may be provided to describe the consistency of CZP absorption from the same participant based on the linear mixed effects model as described in Section 3.1.1.

Data analyses may be conducted on log-transformed data, based on visual inspection of the data. This will be based on visual inspection of histograms, boxplots and quantile-quantile plots for each dosing regimen which will be included as part of the statistical appendices. If the data show a departure from normality, data analysis will be conducted on log transformed data (and back-transformed results displayed).

13.2.16 PK Graphical Displays (Section 9.1.3)

Section header inserted and text for graphics updated to:

The graphs to be produced by dosing regimen include:

1. Individual CZP plasma concentration plots using gestational week with predose and postdose values plotted side by side,
2. Spaghetti plots of CZP plasma concentrations using gestational week with predose and postdose values plotted side by side, and
3. Geometric Mean plots by dosing regimen and sample time relative to dose, i.e., separately for predose and postdose. The time points will be based on trimester as defined in Section 3.2.2, including the postpartum period. The plot will show both a linear and semi-logarithmic scale side by side. The average predose (or postdose) results within trimester per participant will be used to calculate the geometric mean and 95% CI for all participants combined.

13.2.17 Anti-Drug Antibody Methods (Section 9.2.1, Section 9.2.2, and Section 9.2.3)

Section 9.2.1 text updated to:

Anti-drug antibodies (ADA) will be measured using a three-tiered assay approach: screening, confirmatory and titration assay.

Samples will first be evaluated in the screening assay (reported as 'negative screen' or 'positive screen'), followed by analysis of screened positive samples in the confirmatory assay to confirm the true positivity of the samples (reported as 'negative immuno-depletion' or 'positive immuno-depletion'). Samples that are confirmed as positive in the confirmatory assay will be evaluated in a titration assay to quantify the ADA level and will be reported as titer (reciprocal dilution factor including minimum required dilution [MRD]).

The ADA sample status will be determined for each visit where samples were collected for ADA analysis (both scheduled and any unscheduled visits).

Section 9.2.2 text updated to:

Once determined positive, a study participant's highest titer will be used to categorize ("titer classification") the study participant as follows:

- Positive ≤32

- Positive >32 - ≤128
- Positive >128 - ≤512
- Positive >512 - ≤1024
- Positive >1024 - ≤4096
- Positive >4096

Section 9.2.3 text updated to:

The fold difference increase from postpartum value, i.e., the minimum significant ratio (MSR) determined during assay validation, will be reported in the relevant tables, listings and figures. It reflects the fold difference in titer level that is considered higher than the assay variation in titer determination.

The following summaries, figures and listings will be produced using the MSR and will be presented using the SS:

- 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 dose regimen.
- Spaghetti plots of the individual time course plots of ADA titer (y-axis) by time (x-axis) for participants with at least one ADA positive sample status, with one line representing one study participant. Separate plots will be presented for each dose regimen. Plots may be presented using a semi-logarithmic scale for the ADA titers (ADA negative samples will therefore be excluded from the plot). Time will be presented using gestational week.
- Summary statistics of ADA titers (mean, min, max, geomean) per time point and dose regimen.
- Summary of titer classification for all study participants who test positive at any visit will be presented by category.
- The ADA results will be listed including the results from the screening assay, confirmatory assay, and titration assay (titer level), the ADA sample status, the drug concentration with indication if the drug level exceeds the ADA assay tolerance for detecting 100 ng/ml ADA or alternative level as defined above (Y/N).

In addition, the following figures will be produced to illustrate the impact of ADA on PK:

- Spaghetti plots of the individual CZP plasma concentrations (each participant corresponding to a line) over time will be produced on a linear and semi-logarithmic scale according to ADA titer classification. Gestational week should be indicated below the x-axis.
- Time course plots of individual CZP plasma concentrations (one plot per participant) superimposed with the participant's corresponding ADA titer over the course of the study will be presented. Plots may be presented using a semi-logarithmic scale for the ADA titers (ADA negative samples will therefore be excluded from the plot). Time will be presented using gestational week.

13.2.18 TEAE of interest (Section 11.3)

Clarification was added:

Separate tables will be created to summarize each of the above TEAEs of interest by system organ class, high level term, and PT, where the TEAEs of interest are identified using standardized MedDRA queries (SMQ). An additional review cycle to confirm the targeted events will be implemented for opportunistic infections as described in Section 11.3.1.

All TEAEs and serious TEAEs will be listed using the SS. Details of serious TEAEs, TEAEs leading to death or study discontinuation will be listed. For results disclosure on public registries (e.g., ClinicalTrials.gov), TEAEs and serious TEAEs will be published.

13.2.19 Identification of Opportunistic Infections (Section 11.3.1)

Text added:

A summary of opportunistic infections (including tuberculosis) will include all TEAEs identified using UCB-defined search criteria.

Identification Process

The steps below outline 2 ways (both programmatically and after manual review) in which opportunistic infections (or potential opportunistic infections) can be identified using standardized MedDRA queries (SMQ):

Step 1 [programmatic identification]: All TEAEs from 'Opportunistic infections (SMQ)' with a narrow scope are considered as automatically identified opportunistic infection, regardless of seriousness.

Step 2 [manual identification]: All other TEAE in the 'Opportunistic infections (SMQ)' with a broad scope will be evaluated on a case-by-case basis by the study physician to determine whether it is a true opportunistic infection (OI) of interest or not.

Review Process

A final listing for opportunistic infections (in the format described below) will be produced and reviewed by the study physician prior to finalizing the database.

The study programming team will produce an Excel listing of all AEs from the ADaM domain for participants with at least 1 TEAE falling within the broad scope of the 'Opportunistic infections (SMQ)' allowing a review of all the participants' AEs to establish OI of interest. The Excel listing will contain the following columns (using the descriptions below as the column headings in the Excel listing):

- Study ID
- Unique Participant ID
- AE Term (Verbatim)
- AE Preferred Term
- AE System Organ Class

- AE High Level Term
- AE Low Level Term
- Date of Onset
- Outcome of Adverse Event
- Date of Outcome
- TEAE Flag
- Serious Adverse Event?
- Relationship to Study Medication
- Intensity
- Action Taken with IMP
- Opportunistic Infection – Automatic; code and scope (Y/N)
- Opportunistic Infection – Manual Review; code and scope (Y/N)
- Flag for previously reviewed? (NEW/OLD)
- Data Cut Date
- Opportunistic Infection – Final Adjudication (Y/N)

Note the following about the final 5 variables in this listing:

- *Opportunistic Infection – Automatic*: This is flagged as "Y" if the criteria for automatic selection as described in "Step 1" of the identification process are met.
- *Opportunistic Infection – Manual Review*: This is flagged as "Y" if the criteria for case-by-case selection as described in "Step 2" of the identification process are met.
- *Flag* – This has a value of either "NEW" or "OLD". It is marked as "NEW" if the event is appearing for the first time in that run of the listing. Otherwise, if it has appeared previously, it is marked as "OLD". Unique records are determined by USUBJID AESPID for purposes of identifying whether an event has been modified from a previous run.
- *Date* – Only for cases where Flag is "NEW", this field will be populated with the data cut date for that particular run of the listing.
- *Opportunistic Infection – Final Adjudication* – For new events, this is always left blank by the programmers. It will be completed by the study physician for every event that appears in the listing. For events adjudicated as opportunistic, the field will be populated with a "Y".

Following the review by the study physician, the *Opportunistic Infection – Final Adjudication* column will be completed (as described above), and the spreadsheet will be returned to the study programming team via e-mail. The decisions documented in the returned file will be merged with AE data for final reporting in a summary table and flagged in the All Adverse Events listing.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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