CERTOLIZUMAB PEGOL

STATISTICAL ANALYSIS PLAN

Study: PS0017

Product: Certolizumab Pegol

Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in Japanese subjects with moderate to severe chronic psoriasis

SAP/Amendment Number	Date
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACR20/50/70	American College of Rheumatology 20%/50%/70% response criteria
AE	adverse event
AEOI	adverse event of interest
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BM	Blinded Maintenance
BSA	Body surface area
CGI-I	Clinical Global Impression - Improvement
CES	Cohort Enrolled Set
CFAS	Cohort Full Analysis Set
CPKS	Cohort Pharmacokinetic Set
CRP	C-reactive protein
CSR	Clinical Study Report
CSS	Cohort Safety Set
CZP	certolizumab pegol
CTCAE	Common Terminology Criteria for Adverse Events
DAS28(CRP)	Disease Activity Score 28 joint count C-reactive protein
DBP	diastolic blood pressure
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
EM	Escape Maintenance
EPS	Erythrodermic Psoriasis Set
ES	Enrolled Set
EWV	Early Withdrawal Visit
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPPS	Generalized Pustular Set
GGT	gamma-glutamyl transferase
HAQ-DI	Health Assessment Questionnaire-Disability Index

HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonization
IGRA	Interferon-gamma release assay
IMP	investigational medicinal product
IRB	Institutional Review Board
JDA	Japanese Dermatology Association
LDH	lactate dehydrogenase
LLN	lower limit of normal
MCID	Minimally clinically important difference
MCMC	Markov Chain Monte Carlo
mNAPSI	Modified Nail Psoriasis Severity Index
n	number of observations
N	number of subjects
NAPSIS	Nail Psoriasis Severity Index Set
NRI	non-responder imputation
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Activity and Severity Index
PBO	placebo
PD	pharmacodynamics(s)
PDILI	potential drug-induced liver injury
PEG	polyethylene glycol
PGA	Physician's Global Assessment
PGAAP	Patient´s Global Assessment of Arthritis Pain
PhGADA	Physician's Global Assessment of Disease Activity
PGADA	Patient's Global Assessment of Disease Activity
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetics Per-Protocol Set
PPS	Per-Protocol Set
PR	pulse rate
PsA	psoriatic arthritis
PsAS	Psoriatic Arthritis Set
PSO	psoriasis
Q2W	every 2 weeks
Q4W	every 4 weeks
RBC	red blood cell
RF	rheumatoid factor

RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
sc	subcutaneous
SD	standard deviation
SFU	Safety Follow-up
SMQ	Standardised MedDRA Queries
SS	Safety Set
TE-ADA	treatment emergent anti-drug antibody
TB	tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide all information that is necessary to perform the required interim and final statistical analysis of PS0017. It also defines the summary tables, listings and figures to be included in the final clinical study report according to protocol.

The SAP is based on the following study documents: Final protocol, 23 Sep 2016, Protocol Amendment 1, 11 Oct 2016, Protocol Amendment 2, 22 Nov 2016, Protocol Amendment 3, 11 Apr 2017, and Protocol Amendment 4, 25 Jan 2018.

The structure and content of this SAP provides sufficient details to meet the requirements identified by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA) (ICH Guidance on Statistical Principles for Clinical Trials [E9]).

2 PROTOCOL SUMMARY

PS0017 is a randomized, double-blind, parallel group, placebo (PBO)-controlled, multicenter study designed to evaluate the efficacy and safety of certolizumab pegol (CZP) in adult Japanese subjects with moderate to severe chronic plaque psoriasis (PSO). In addition, a cohort of subjects with generalized pustular PSO or erythrodermic PSO will be eligible for the study.

Approximately 125 subjects with moderate to severe chronic plaque PSO, including psoriatic arthritis (PsA), will be randomly assigned in a 2:2:1 ratio at Baseline to either CZP 400mg every 2 weeks (Q2W), CZP 200mg Q2W (loading dose of CZP 400mg at Weeks 0, 2, and 4), or PBO. Subject treatment assignment will be stratified by prior biologic exposure (yes/no) and psoriatic arthritis (yes/no). Study drug will be administered by subcutaneous (sc) injection. Subjects will be followed in a blinded fashion up to Week 52 following randomization.

The treatment from Week 16 through Week 52 for subjects who achieve a Psoriasis Activity and Severity Index (PASI) 50 response will be based on response to double-blind treatment at Week 16. Subjects randomized to CZP 400mg Q2W will remain on their assigned dose. Subjects initially randomized to CZP 200mg Q2W will be re-randomized (1:1) to receive either CZP 200mg Q2W or CZP 400mg Q4W (with PBO administered on alternate dosing weeks to maintain the blind). Subjects randomized to PBO treatment who achieve a PASI50 response at Week 16 will continue on PBO. Subjects who do not achieve a PASI50 response at Week 16 will escape from double-blind treatment and enter the open-label arm of the study.

Subjects who do not achieve a PASI50 response at the Week 16, 24, 32, or 40 visit will escape from double-blind treatment and enter the open-label arm of the study. These subjects will receive open-label CZP (400mg Q2W as 3 loading doses followed by CZP 200mg Q2W) from the visit the response criterion is not met. Subjects receiving open-label CZP 200mg Q2W in the escape arm and not achieving a PASI50 response will be allowed to have their dose increased to CZP 400mg Q2W at the visit the criterion is not met, at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit (eg, a PASI50) at the 400mg Q2W dose, the subject should be withdrawn from the study.

A cohort of subjects with generalized pustular PSO or erythrodermic PSO will be eligible for the study. At least 10 subjects with generalized pustular PSO or erythrodermic PSO will be randomly assigned in a 1:1 ratio at Baseline to open-label CZP 400mg Q2W or CZP 200mg

Q2W (loading dose of CZP 400mg at Weeks 0, 2, and 4). Study drug will be administered by sc injection.

The treatment from Week 16 through Week 52 for the cohort of subjects with generalized pustular PSO or erythrodermic PSO will be based on response to open-label treatment at Week 16. Subjects achieving a "much improved" or "very much improved" in the Global Improvement Score (for subjects with generalized pustular PSO) or a PASI50 response (for subjects with erythrodermic PSO) will continue to receive the same treatment as randomized. Subjects in the CZP 200mg Q2W group who are not in response (not achieving "much improved" or "very much improved" in the Global Improvement Score [for subjects with generalized pustular PSO] or a PASI50 response [for subjects with erythrodermic PSO]) will be allowed to have their dose increased to CZP 400mg Q2W, at the discretion of the Investigator. Subjects randomized to CZP 400mg Q2W will continue to receive CZP 400mg Q2W at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit at the 400mg Q2W dose, the subject could be withdrawn from the study.

All subjects, including those withdrawn from the study treatment, will have a Safety Follow-Up (SFU) Visit 10 weeks after their final dose of study medication.

2.1 Study objectives

2.1.1 Primary objective

The primary objective of the study is to demonstrate the efficacy of CZP administered sc at the doses of CZP 400mg Q2W and CZP 200mg Q2W (after a loading dose of CZP 400mg at Weeks 0, 2, and 4) in the treatment of moderate to severe chronic plaque PSO in Japan.

2.1.2 Secondary objectives

The secondary objectives of the study are to assess:

- The optimal initial treatment dose for the treatment of moderate to severe chronic plaque PSO
- Durability of the clinical response with maintenance treatment
- The safety and tolerability of CZP
- Improvement of skin-related quality of life
- Change from Baseline in Itch Numeric Rating Scale at Week 16

2.1.3 Other objectives

The other objectives of the study are to demonstrate the effects of CZP on other aspects of disease:

- Efficacy for PsA disease in the subgroup of affected subjects at Baseline
- Efficacy for psoriatic nail disease in the subgroup of subjects with nail disease at Baseline
- Efficacy and safety in a cohort of patients with erythrodermic PSO or generalized pustular PSO
- Safety and efficacy of long-term use of CZP
- Pharmacokinetics and immunogenicity of CZP

2.2 Study variables

2.2.1 Primary efficacy variables

The primary efficacy variable for subjects with moderate to severe chronic plaque PSO is:

- PASI75 at Week 16

For subjects with erythrodermic PSO or generalized pustular PSO, no primary efficacy variables are planned.

2.2.2 Secondary efficacy variables

The secondary efficacy variables for subjects with moderate to severe chronic plaque PSO are:

- Physician's Global Assessment clear or almost clear (with at least 2-category improvement) at Week 16
- PASI90 at Week 16
- Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 16
- Change from Baseline in Itch Numeric Rating Scale at Week 16

For subjects with erythrodermic PSO or generalized pustular PSO, no secondary efficacy variables are planned.

2.2.3 Other efficacy variables

The other efficacy variables are listed below and will be evaluated at scheduled visits as outlined in Section 13.1. This excludes the primary and secondary variables (and corresponding time points) that have already been specified above as primary or secondary efficacy variables.

2.2.3.1 Other efficacy variables for subjects with moderate to severe chronic plaque PSO

Double-Blind Overall population (subjects with moderate to severe chronic plaque PSO)

- PASI75 at Week 24 and Week 52
- PASI50, PASI75, PASI90, and PASI100
- PGA clear or almost clear (with at least 2-category improvement)
- Absolute and percent change from Baseline in PASI score
- PGA score distribution
- Time to onset of action, defined as the time to PASI50
- Time to onset of action, defined as the time to PASI75
- Time to onset of action, defined as the time to PASI90
- Time to onset of action, defined as the time to PASI100
- Absolute and percent change from Baseline in the body surface area (BSA) affected by PSO

- Change from Baseline in DLQI mean scores, percent of subjects achieving minimal clinically important difference (MCID), and percent achieving DLQI remission
- Change from Baseline in Itch Numeric Rating Scale mean scores and percent of subjects achieving MCID

Double-Blind PsA population

- American College of Rheumatology 20, 50, 70% response criteria (ACR20, 50, 70) and change from Baseline in all individual ACR core components in the subpopulation of subjects with PsA at Baseline

1. A subject will be considered an ACR20/50/70 responder if:
   1) The count for both Tender joint count (TJC) and swollen joint count (SJC) (68/66 joint counts) (Section 8.3.10) have reduced by 20/50/70% or more, respectively, from the Baseline assessment and
   2) At least 3 out of the following 5 assessments show reduction of 20/50/70% or more, respectively, from the Baseline assessment:
   – Physician's Global Assessments of Disease Activity (PhGADA, Section 8.3.11),
   – Patient's Global Assessments of Disease Activity (PGADA, Section 8.3.12),
   – Patient's Global Assessment of Arthritis Pain (PGAAP, Section 8.3.13),
   – Health Assessment Questionnaire Disability Index (HAQ-DI, Section 8.3.14),
   – C-reactive protein (CRP).

- Change from Baseline in Disease Activity Score 28 joint count C-reactive protein (DAS28(CRP), Section 8.3.15)

Double-Blind NAPSI population

- Change from Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) in the subpopulation of subjects with nail disease at Baseline

Overall Escape population

- PASI50, PASI75, PASI90, and PASI100
- PGA clear or almost clear (with at least 2-category improvement)
- Absolute and percent change from Baseline in PASI score
- PGA score distribution
- Absolute and percent change from Baseline in the BSA affected by PSO
- Change from Baseline in DLQI mean scores, percent of subjects achieving MCID, and percent achieving DLQI remission
- Change from Baseline in Itch Numeric Rating Scale mean scores and percent of subjects achieving MCID
- American College of Rheumatology 20, 50, 70% response criteria (ACR20, 50, 70) and change from Baseline in all individual ACR core components in the subpopulation of subjects with PsA at Baseline

- Change from Baseline in Disease Activity Score 28 joint count C-reactive protein (DAS28(CRP), Section 8.3.15) in the subpopulation of subjects with PsA at Baseline
- Change from Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) in the subpopulation of subjects with nail disease at Baseline

2.2.3.2 Other efficacy variables for subjects with erythrodermic PSO or generalized pustular PSO

Cohort overall population (subjects with erythrodermic PSO or generalized pustular PSO)

- Clinical Global Impressions of Improvement (CGI-I)
- Change from Baseline in DLQI mean scores, percent of subjects achieving MCID, and percent achieving DLQI remission
- Change from Baseline in Itch Numeric Rating Scale mean scores and percent of subjects achieving MCID

Cohort generalized pustular PSO population

- Global Improvement Score
- Japanese Dermatological Association (JDA) severity index score

Cohort erythrodermic PSO population

- PASI50, PASI75, PASI90, and PASI100
- PGA clear or almost clear (with at least 2-category improvement)
- Absolute and percent change from Baseline in PASI score
- PGA score distribution
- Absolute and percent change from Baseline in the BSA affected by PSO

2.2.4 Pharmacokinetic/pharmacodynamic variable

- Plasma CZP concentration prior to and during study treatment

2.2.5 Immunological variable

- Plasma anti-CZP antibody levels prior to and during study treatment

2.2.6 Safety variables

Safety variables to be assessed are:

- AEs
- Blood pressure
- Physical examination
- Clinical laboratory values (hematology, biochemistry, and urinalysis)
- Interferon-gamma release assay (IGRA) test for tuberculosis (TB)

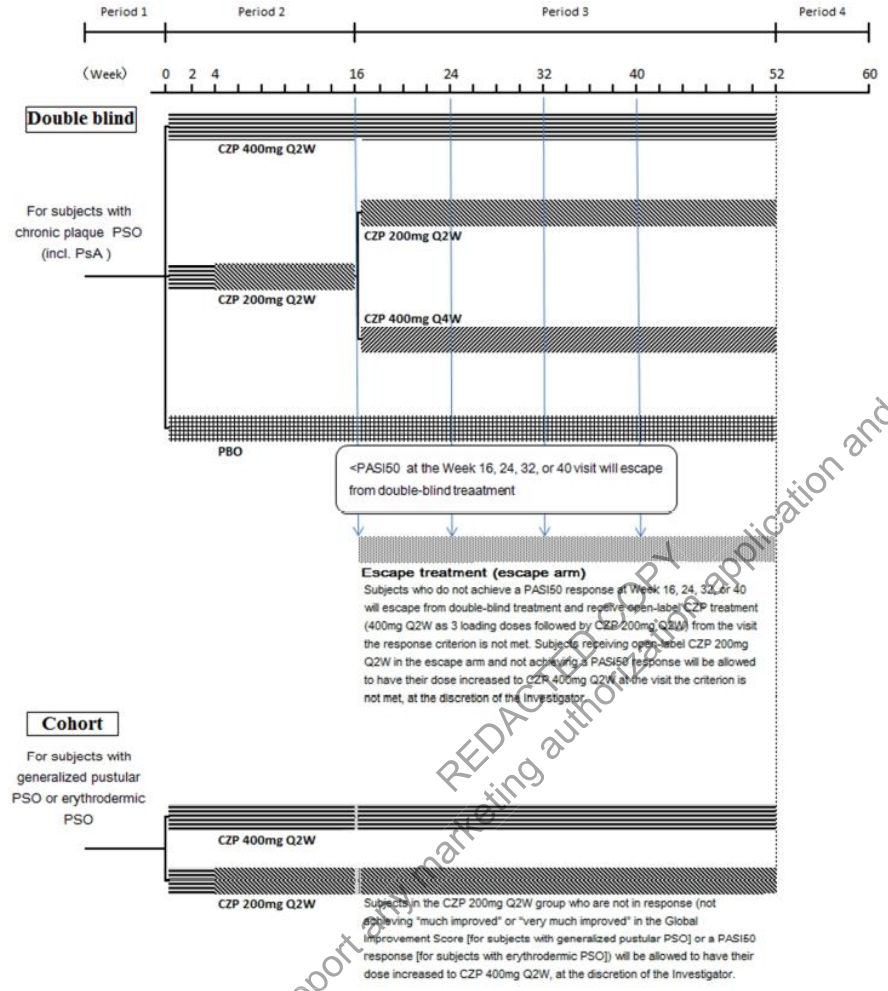
2.3 Study design and conduct

This is a Phase 2/3, multicenter, randomized, double-blind, PBO-controlled, parallel-group study designed to evaluate the efficacy and safety of CZP in adult subjects with moderate to

severe chronic PSO, including PsA, in Japanese subjects. In addition, a cohort of subjects with erythrodermic PSO or generalized pustular PSO will be eligible to receive open-label treatment in the study.

The study includes 4 periods. Figure 2-1 provides a schematic of the study design.

Figure 2–1: PS0017 study design



If the Investigator determines that the subject is no longer benefiting from CZP treatment, the subject should complete the Early Withdrawal Visit (EWV) and return to the site for a SFU Visit 10 weeks after his/her final dose of study drug.

2.3.1 Study design for subjects with moderate to severe chronic plaque PSO

2.3.1.1 Period 1: Screening

The Screening Period of 2 to 5 weeks will be used to confirm eligibility; obtain laboratory data; verify that the doses of nonsteroidal anti-inflammatory drugs (NSAIDs) and other pain relievers, such as acetaminophen, paracetamol, or mild opiates, if used to treat PsA are stable; and enable washout of any medications not permitted for use during the study.

2.3.1.2 Period 2: Initial Period - Week 0 to Week 16

Eligible subjects will be allocated to the following study treatments in a 2:2:1 ratio:

- CZP 400mg Q2W (n=50): CZP administered sc at the dose of CZP 400mg Q2W

- CZP 200mg Q2W (n=50): CZP administered sc at the dose of CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg Q2W (starting at Week 6)
- PBO (n=25): PBO administered sc Q2W

Study treatments (including PBO) will be administered by dedicated, unblinded, trained site personnel at Baseline and Q2W thereafter to Week 14. Week 16 is the last study visit during this period.

2.3.1.3 Period 3: Maintenance Period - Week 16 to Week 52

The treatment received in Period 3 will be based on response to double-blind treatment at Week 16. All CZP and PBO treatments will be administered by dedicated, unblinded, trained site personnel at site visits, excluding the escape treatment.

Subjects who achieve a PASI50 response at Week 16 will continue therapy as follows:

- Subjects initially randomized to CZP 400mg Q2W will continue to receive CZP 400mg Q2W.
- Subjects initially randomized to CZP 200mg Q2W will be re-randomized (1:1) to receive either CZP 200mg Q2W or CZP 400mg Q4W (with PBO administered on alternate dosing weeks to maintain the blind).
- Subjects initially randomized to PBO will continue to receive PBO.

Subjects who do not achieve a PASI50 response at Week 16, 24, 32, or 40 will escape from double-blind treatment and receive treatment as follows:

- Escape treatment: Subjects entering the escape arm of the study will receive open-label CZP treatment (400mg Q2W as 3 loading doses followed by CZP 200mg Q2W). Subjects receiving open-label CZP 200mg Q2W in the escape arm and not achieving a PASI50 response will be allowed to have their dose increased to CZP 400mg Q2W, at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit (eg, a PASI50) at the CZP 400mg Q2W dose, the subject should be withdrawn from the study.

2.3.1.4 Period 4: Safety Follow-up: Week 52 to Week 60

All subjects, including those withdrawn from study treatment, will have a Safety Follow-Up Visit, 10 weeks after their final dose of study medication.

2.3.2 Study design for subjects with erythrodermic PSO or generalized pustular PSO

2.3.2.1 Period 1: Screening

The Screening Period of 2 to 5 weeks will be used to confirm eligibility and obtain laboratory data.

2.3.2.2 Period 2: Initial Period - Week 0 to Week 16

At least 10 subjects in the cohort with erythrodermic PSO or generalized pustular PSO will be allocated in a 1:1 ratio to the following open-label study treatments:

- CZP 400mg (n ≥5): CZP administered sc at the dose of CZP 400mg Q2W
- CZP 200mg (n ≥5): CZP administered sc at the dose of CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg Q2W (starting at Week 6)

2.3.2.3 Period 3: Maintenance Period - Week 16 to Week 52

The treatment received in Period 3 will be based on the initial study treatment and on response to open-label treatment at Week 16:

- Subjects achieving a "much improved" or "very much improved" in the Global Improvement Score (for subjects with generalized pustular PSO) or a PASI50 response (for subjects with erythrodermic PSO) will continue to receive the same treatment as randomized.
- Subjects in the CZP 200mg Q2W group who are not in response (not achieving "much improved" or "very much improved" in the Global Improvement Score [for subjects with generalized pustular PSO] or a PASI50 response [for subjects with erythrodermic PSO]) will be allowed to have their dose increased to CZP 400mg Q2W, at the discretion of the Investigator. Subjects randomized to CZP 400mg Q2W will continue to receive CZP 400mg Q2W at the discretion of the Investigator. If, in the opinion of the Investigator, the subject is not receiving benefit at the 400mg Q2W dose, the subject could be withdrawn from the study. Per the Withdrawal Criteria, subjects who develop an aggravation of the primary disease or concomitant disease with hospitalization in the opinion of the Investigator must be withdrawn from the study.

2.3.2.4 Period 4: Safety Follow-up: Week 52 to Week 60

All subjects, including those withdrawn from study treatment, will have a Safety Follow-Up Visit, 10 weeks after their final dose of study medication.

2.3.3 Study duration per subject

The study duration for each subject is estimated to be up to 65 weeks as follows:

- Up to 5 weeks of Screening (Period 1)
- 16 weeks in the Initial Period (Period 2)
- 36 weeks in the Maintenance Period (Period 3)
- Safety Follow-Up Visit 10 weeks after final dose of study drug (Period 4)

The end of the study is defined as the date of the final visit of the final subject in the study.

2.3.4 Planned number of subjects, region and sites

Approximately 125 subjects with moderate to severe chronic plaque PSO will be randomized. In addition, a cohort of ≥10 subjects with erythrodermic PSO or generalized pustular PSO will be enrolled. The planned number of study sites is approximately 35. The study sites will be located in Japan.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All statistical analyses will be performed according to Chiltern Standards Operating Procedures using SAS® Version 9.3 or higher.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis for the respective treatment group, subset, period, and visit, if available. Unless otherwise noted, all percentages will be displayed to 1 decimal

place. No decimal will be presented when the percentage is 100%. For data points with n=0 (i.e., no subjects in the applicable category), no value for percentage of subjects will be displayed. Missing observations will be included. Thus, percentages always add up to 100% at each visit. For the shift tables, the denominator used for the calculation of percentages will be the number of subjects in the appropriate analysis set.

For continuous variables, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. 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 data.
- Minimum and maximum will have the same number of decimal places as the original value.

All descriptive statistics will be presented by treatment where applicable, using the available data for the study population as observed. All tabulations will be sorted by treatment, parameter, period and visit (including time relative to dosing if applicable, unless otherwise stated). Only scheduled visits and times relative to dosing will be included in the tabulation. The minimum post-baseline and maximum post-baseline values included in certain analyses by visit are not specific time points; rather they are the minimum and maximum observed non-missing values per subject during PS0017 or in a special period, if appropriate, inclusive of all scheduled and unscheduled visits. If multiple visits fulfill the minimum/maximum criteria, the earlier visit will be flagged to have the minimum/maximum post-baseline value.

The variables will be presented for the subjects with moderate to severe chronic plaque PSO and for the subjects with erythrodermic PSO or generalized pustular PSO, if available, using the appropriate analysis set. Data of the Initial Period and of the Maintenance Period will tabulated by treatment group and overall. Data of the Maintenance period will also be displayed for the escape arm.

Statistical tests of efficacy variables will be presented as 2-sided p-values 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."

Unless otherwise stated, listings will be sorted by treatment (PBO, then the CZP treatment groups), subject number within treatment group (not randomization number), parameter (if applicable) and visit (if applicable; including timing relative to dosing if applicable). For listings including nonrandomized subjects, the nonrandomized subjects will be shown first in the listing, ordered by subject number. All listings will include repeated 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. Data for derived time points Last Visit and Early Withdrawal will also be included in subject data listings. Dates will be presented in the listings in the format 'YYYY-MM-DD' and times will be presented in 24h clock format as 'hh:mm' or 'hh:mm:ss' where appropriate.

3.2 General study level definitions

3.2.1 Analysis time points

All data will be analyzed based on the nominal time points, without mapping to analysis visit windows. If subjects have more than one observation for a given time point, the observation

closest to the intended time point will be used. If both observations are equidistant from the intended time point, then the later value will be used. This rule applies to efficacy data. For safety data, if there is a repeat evaluation, the repeat (latest) data will be used.

The time points for individual assessments are provided in Table 13–1, Section 13.1.

3.2.2 Relative day

The relative day will be calculated for each of the 4 study periods as follows:

Relative day 1 is the date of first study drug (CZP/PBO) administration.

Relative day of date X = date X - Date of first study drug administration +1 if date X is on or after date of first study drug administration and on or before Date of last study drug administration.

Relative day of date X = date X - Date of first study drug administration if date X is before date of first study drug administration.

Relative days before first study drug administration will have the prefix "-".

Relative day after last dose of study drug administration will have the prefix "+" and will be calculated from the date of last study drug administration (date X - date of last study administration).

Calculations of "Relative Day" should not include partial dates but should be left blank in these instances.

In the case of AEs, relative days for start and stop dates will be calculated as number of days since the first injection of study medication. In addition to the relative days since first injection of study medication, the relative days since the last/latest injection of study medication will be calculated.

3.2.3 Study periods

The end of the study is defined as the date of the last visit of the last subject in the study. Subjects are considered to have completed the study if they completed the Week 52 study visit, not including SFU visit. The study was designed with 4 periods, and data will be assigned to these study periods based on the windows shown in Table 3–1. The label column in this table is the naming convention that will be used to identify the periods included in the analysis tables, figures, and listings. Of particular relevance for this SAP are the Initial Period and the Maintenance Period.

Table 3–1: Study period description and windowing

Period	Description	Label	Window
Period 1	Screening	Screening Period	Up to the date of Randomization - 1 day
Period 2[a]	16 Week Double-Blind Phase	Initial Period	Date of Randomization to date of Week 16 visit
Period 3	36 Week Double-Blind Phase	Maintenance Period	Date of Week 16 visit +1 day to date of Week 52 visit
Period 4[b]	8 Week SFU, 10 Weeks after last dose	SFU Period	Date of Week 52 visit +1 day to date of Week 60 visit

[a] In general, safety, laboratory and efficacy data collected up to Week 16 of the study belongs to Period 2. The study drug injection at Week 16 and subsequent data collected at future visits (up to Week 52) correspond to Period 3.
[b] Or if early discontinuation, date of last visit prior to safety visit +1 day to date of Safety Follow-up visit.

For summaries where the time period from Baseline (Week 0) to Week 52 is of interest, that will be referred to as the Combined Initial and Maintenance Period. A subject will be considered to have completed a period if they complete the last scheduled study visit for that period.

3.2.4 Mapping of assessments performed at Early Discontinuation Visit

Study assessments at an early withdrawal visit will be assigned to the next scheduled site visit following the last visit where assessments were available regardless of if the actual early withdrawal visit date matches another scheduled visit date. The early withdrawal visit re-mapping is not done for pharmacokinetics and anti-CZP antibodies.

3.2.5 Subjects switching centers during the study

Subjects changing center during the study will be allocated to the initial center throughout the study.

3.3 Definition of Baseline values

The last value obtained prior to the first administration of study drug will be used as the baseline value. If there is evidence that measurements taken on the same day as administration of first study medication were actually taken after this administration, then only values strictly prior to that date should be used for that subject.

If a Baseline measurement is missing or not collected, and a Screening value is available, the Screening value will be utilized as the Baseline.

Baseline values for composite scores should be computed using components from the same visit where the relevant measurements were recorded prior to dosing. For example, if the Screening visit has all of the components, but the Baseline visit is missing one or more components, the Baseline value for the component score should be calculated using the Screening visit values.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, on the primary efficacy, key safety, or pharmacokinetic (PK)/pharmacodynamic (PD) outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. All protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented in a separate Protocol Deviation Tracker prior to unblinding to confirm exclusion from analysis sets.

3.5 Analysis sets

The analysis sets for subjects with moderate to severe chronic plaque PSO are shown below in Section 3.5.1 to Section 3.5.10. The analysis sets for subjects with generalized pustular PSO or erythroid PSO are shown in Section 3.5.11 to Section 3.5.18.

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects with plaque PSO who have given informed consent (non-cohort subjects).

3.5.2 Randomized Set

The Randomized Set (RS) will consist of all subjects with plaque PSO randomized into the double-blind part of the study.

3.5.3 Safety Set

The Safety Set (SS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the RS who received at least 1 dose of the study medication and have valid efficacy assessments for baseline and for at least 1 post baseline visit.

3.5.5 Per Protocol Set

The Per-Protocol Set (PPS) will consist of subjects in the FAS who have completed a minimal exposure of 16 weeks to the treatment regimen without any important protocol deviations that may influence the validity of the data for the primary efficacy variable. Important protocol deviations will be predefined and evaluated during a data evaluation meeting prior to unblinding of the data.

The criteria for important protocol deviations leading to exclusion from the PPS will be discussed and appropriately documented (see Section 3.4).

3.5.6 Pharmacokinetics Per-Protocol Set

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all subjects in the RS who took at least 1 dose of the study medication and provided at least 1 quantifiable CZP plasma concentration while receiving blinded treatment.

The criteria for important protocol deviations leading to exclusion from the PK-PPS will be discussed and appropriately documented (see Section 3.4).

3.5.7 PsA Set

The PsA Set (PsAS) will consist of subjects in the FAS who have PsA disease at Baseline.

3.5.8 NAPSI Set

The NAPSI Set (NAPSIS) will consist of subjects in the FAS with nail disease at Baseline.

3.5.9 Blinded Maintenance Set

The Blinded Maintenance (BM) Set is defined as follows: Analyses based on either SS, FAS, PPS, PsAS, NAPSI will be based on BM SS, BM FAS, BM PPS, BM PsAS or BM NAPSI for the Interim Analysis, where the BM Set will consist of all subjects in the respective analysis set who do not discontinue treatment during Initial Period and who are PASI 50 responder at week 16 (do not escape planned treatment). All analysis sets with prefix BM are based on these additional conditions.

For final analysis, analyses based on BM sets will include all data observed during blinded treatment only (including data at escape visit, if applicable). Escapers at Week 16 will be included in tables by blinded maintenance treatment with their observed value at Week 16 and imputed data after escape. This is different as done for Interim Analysis which did not take escapers into account.

3.5.10 Escape Maintenance Set

The Escape Maintenance (EM) Set is only applicable for the final analysis. Analysis sets EM SS, EM FAS, EM PsAS and EM NAPSI are introduced for the final analysis, where the EM Set will consist of all subjects in the respective analysis set (SS, FAS, PsAs and NAPSI) who do not discontinue treatment during Initial Period and who have received at least 1 dose of escape study medication during the Maintenance Period. Analyses based on EM sets will include only data observed during escape treatment.

3.5.11 Cohort Enrolled Set

The Cohort Enrolled Set (CES) will consist of subjects with erythrodermic PSO or generalized pustular PSO who have given informed consent.

3.5.12 Cohort Randomized Set

The Cohort Randomized Set (CRS) will consist of subjects with erythrodermic PSO or generalized pustular PSO randomized into the cohort.

3.5.13 Cohort Safety Set

The Cohort Safety Set (CSS) will consist of subjects with erythrodermic PSO or generalized pustular PSO in the CRS who have received at least 1 dose of study medication.

3.5.14 Cohort Full Analysis Set

The Cohort Full Analysis Set (CFAS) will consist of subjects in the CRS who received at least 1 dose of the study medication, subjects with generalized pustular PSO have valid efficacy assessment (JDA score) for baseline and for at least 1 post baseline visit, or subjects with erythrodermic PSO have valid efficacy assessments (PASI score) for baseline and for at least 1 post baseline visit.

3.5.15 Cohort Pharmacokinetics Set

The Cohort Pharmacokinetics Set (CPKS) will consist of subjects with erythrodermic PSO or generalized pustular PSO randomized into the cohort who took at least 1 dose of the study medication and provided at least 1 quantifiable CZP plasma concentration.

3.5.16 Erythrodermic PSO Set

The Erythrodermic PSO Set (EPS) will consist of subjects in the CFAS with erythrodermic PSO disease at Baseline.

3.5.17 Generalized Pustular PSO Set

The Generalized Pustular PSO Set (GPPS) will consist of subjects in the CFAS with generalized pustular PSO disease at Baseline.

3.6 Treatment assignment and treatment groups

All safety analyses and pharmacokinetic analyses will be based on actual treatment assignment, whereas all efficacy analyses will be based on randomized treatment assignment, unless specified otherwise. Analyses for escapers will be based on Escape Maintenance Treatment Group or on the latest dose of study medication the subject received before escape.

3.6.1 Subjects with plaque PSO

Period 2 – Initial Period - Week 0 to Week 16

Efficacy and Safety Evaluations:

During the 16-week Period 2, efficacy and safety data will be presented by the following treatment groups:

- PBO
- CZP 200mg Q2W
- CZP 400mg Q2W

Selected variables (where stated in the following sections) may be summarized by treatment group and subgroup (Definition of subgroups, see Section 4.8).

Period 3 – Maintenance Period - Week 16 to Week 52

Efficacy Evaluations – Blinded Maintenance Period:

During the 36-week Period 3, subjects will be allocated to dose groups based on their Week 16 PASI50 response. For efficacy, data will be summarized separately for those subjects remaining in the blinded part of the study (including data at escape visit if applicable) and those subjects who switched to the Escape Arm. For those in the blinded part of the study, efficacy data will be summarized based upon the treatment group assigned at Week 0 and the treatment group assigned at Week 16, using the following blinded maintenance treatment groups:

- PBO/PBO
- CZP 200mg Q2W/CZP 200mg Q2W + CZP 200mg Q2W/CZP 400mg Q4W
- CZP 400mg Q2W/CZP 400mg Q2W
- CZP 200mg Q2W/CZP 200mg Q2W
- CZP 200mg Q2W/CZP 400mg Q4W

Subjects who escape during the Maintenance Period will be displayed until their escape visit using the treatment groups listed above. Placebo escapers at Week 16 will be presented in PBO/PBO, escapers at Week 16 from CZP 200mg Q2W in CZP 200mg Q2W/CZP 200mg Q2W and escapers at Week 16 from CZP 400mg Q2W in CZP 400mg Q2W/CZP 400mg Q2W.

For efficacy, when data will be modelled (logistic regression), the combined treatment group 'CZP 200mg Q2W/CZP 200mg Q2W + CZP 200mg Q2W/CZP 400mg Q4W' will be dropped, because otherwise, subjects would be included twice and this would result in non-independent records and in violation of modelling assumptions.

For the interim analysis, the blinded maintenance treatment groups will be used within the Blinded Maintenance Set (Maintenance Period does not include any information for escapers in interim analysis).

For the final analysis, efficacy data collected during the Maintenance Period while on blinded treatment (including the visit on which the first escape study medication is administered) will be summarized by blinded maintenance treatment group in stand-alone tables based on Blinded Maintenance analysis set.

Efficacy Evaluations – Escape Arms:

Efficacy data collected during the Maintenance Period after the point of escape will be summarized in stand-alone tables using treatment groups consisting of the (re-)randomized treatment before escape and the escape information:

- PBO/Esc CZP
- CZP 200mg Q2W/Esc CZP
- CZP 400mg Q2W/Esc CZP
- CZP 400mg Q4W/Esc CZP

or/and using the following Escape Maintenance Treatment Groups:

- Esc CZP 200mg Q2W
- Esc CZP 400mg Q2W
- All Esc CZP (only for safety data)

Safety Evaluations - Blinded Maintenance Period:

Safety data of the Maintenance Period will be summarized by the following blinded treatment groups (include data only until escape if subject escapes; escape visit date inclusive unless it is an injection site reaction).

- PBO
- CZP 200mg Q2W
- CZP 400mg Q4W
- CZP 200mg Q2W + CZP 400mg Q4W
- CZP 400mg Q2W
- All CZP

Safety Evaluations - Escape Arms:

For those subjects who moved to the Escape Arm during Maintenance Period, safety data after the escape visit will be presented by the following escape maintenance treatment groups:

- Esc CZP 200mg Q2W
- Esc CZP 400mg Q2W
- All Esc CZP (only for safety data)

Combined Initial and Maintenance Period – Week 0 to Week 52

Selected efficacy data for the combined Initial and Maintenance Period will be summarized by randomized treatment group and maintenance treatment group.

Selected safety data for the combined Initial and Maintenance Period will be summarized using two different approaches. In the first approach, data will be summarized by the following blinded treatment groups (including data only until escape if subject escapes; escape visit date inclusive unless it is an injection site reaction):

- PBO
- CZP 200mg Q2W
- CZP 400mg Q4W
- CZP 200mg Q2W + CZP 400mg Q4W
- CZP 400mg Q2W

- All CZP

In the second approach, data will be summarized by the following treatment groups and regardless of whether the dose was administered as blinded or open-label treatment.

- PBO
- CZP 200mg Q2W
- CZP 400mg Q4W
- CZP 200mg Q2W + CZP 400mg Q4W
- CZP 400mg Q2W
- All CZP

3.6.2 Subjects with erythrodermic PSO or generalized pustular PSO

Period 2 – Initial Period - Week 0 to Week 16

Efficacy and Safety Evaluations:

Efficacy and Safety data will be presented by the following randomized treatment groups:

- Erythrodermic PSO CZP 200mg Q2W
- Erythrodermic PSO CZP 400mg Q2W
- Erythrodermic PSO All CZP (only for safety data)
- Generalized Pustular PSO CZP 200mg Q2W
- Generalized Pustular PSO CZP 400mg Q2W
- Generalized Pustular PSO All CZP (only for safety data)
- All Subjects (only for safety data)

Selected parameters (where stated in the following sections) may be summarized by treatment group and subgroup (Definition of subgroups, see Section 4.8).

Period 3 – Maintenance Period - Week 16 to Week 52

Efficacy Evaluations:

During the 36-week Period 3, subjects will be allocated to dose groups based on their Week 16 PASI50 response/Global Improvement Score, as appropriate based on PSO type, and whether or not the subject ever up-titrated their dose during the Maintenance Period. Efficacy data will be summarized based on the following maintenance treatment groups:

- Erythrodermic PSO CZP 200mg Q2W/CZP 200mg Q2W – includes subjects who remained on CZP 200mg Q2W for the duration of both periods
- Erythrodermic PSO CZP 400mg Q2W/CZP 400mg Q2W – includes subjects who remained on CZP 400mg Q2W for the duration of both periods
- Erythrodermic PSO CZP 200mg Q2W/CZP 400mg Q2W – includes subjects who up-titrated to CZP 400mg Q2W at any point during the Maintenance Period
- Generalized Pustular PSO CZP 200mg Q2W/CZP 200mg Q2W – includes subjects who remained on CZP 200mg Q2W for the duration of both periods

- Generalized Pustular PSO CZP 400mg Q2W/CZP 400mg Q2W – includes subjects who remained on CZP 400mg Q2W for the duration of both periods
- Generalized Pustular PSO CZP 200mg Q2W/CZP 400mg Q2W – includes subjects who up-titrated to CZP 400mg Q2W at any point during the Maintenance Period

Safety Evaluations:

For safety analysis, data of the Combined Initial and Maintenance Period will be summarized using the same treatment groups as listed for the Initial Period. Additionally, all Generalized Pustular PSO, all Erythrodermic PSO and all subjects will be summarized.

3.7 Center pooling strategy

All results will be summarized across centers and will not be stratified by center. There will be no specific pooling strategy.

3.8 Coding dictionaries

All AEs, concomitant diseases, and medical history will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA)® coding dictionary, version 18.1 or higher. Prior and concomitant medications will be coded for analysis using the World Health Organization Drug dictionary (WHO-DD), version SEP/2015. As the dictionary version may change during the course of a study, the actual version of coding dictionaries in use at the end of this study will be identified on the table.

3.9 Changes to protocol-defined analyses

The definitions of the Analysis Sets have been clarified.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

For the analysis of the primary, secondary and other key efficacy endpoints (PASI50, e.g. PASI100), prior biologic exposure (yes/no) will be included as factor in the statistical model. Prior biologic exposure is a stratification variable used in the randomization and is included in the analysis as this may have an impact on the efficacy of treatment. The analysis of the secondary endpoints DLQI score at Week 16 and Itch Numeric Rating Scale at Week 16 will include prior biologic exposure as well as the Baseline score as a covariate. Inclusion of the Baseline score will account for any potential Baseline imbalance.

4.2 Handling of dropouts or missing data

PASI 75/50/90/100 and PGA:

- Initial Period

Missing data for the primary variable and other key efficacy variables (eg, PASI50, PASI90, PASI100, and PGA) will be handled using the Markov Chain Monte Carlo (MCMC) method for multiple imputation. Sensitivity analyses which apply different methods of handling missing data for the primary endpoint are planned. Further details are provided in Section 8.1.3.

- Maintenance Period

Subjects can switch to the CZP 200mg Escape Arm (400mg Q2W as 3 loading doses followed by CZP 200mg Q2W) due to lack of PASI50 response at multiple time points (at Week 16 or later). They are treated as non-responders from the time of escape onwards for by

blinded maintenance group tables. Observed PASI50 responses after escape are only relevant for Escape Arm outputs. Other missing data will be handled using the MCMC method for multiple imputation.

Missing data after escape because of discontinuation after escape will be imputed accordingly.

For the cohort missing data will be imputed accordingly, and summaries will be based on MCMC imputed data and on observed case data over time.

Other Binary Efficacy Variables:

- Initial Period

Other binary efficacy variables that are summarized without statistical modeling will use non-response imputation (NRI) as the method for handling missing data. Non-responder imputation (NRI) is a method for dichotomous ("yes (1) or no (0)") or categorical variables, where a subject is considered a non-responder if certain criteria are met. Typically, if a subject drops out of a study, that subject is analyzed as a non-responder, regardless of whether or not the subject was responding to treatment at the time of dropout.

- Maintenance Period

Other binary efficacy variables that are summarized without statistical modeling will use NRI as the method for handling missing data. Escapers will be treated as non-responders from the time of escape onwards for by blinded maintenance group tables. Observed data after escape is only relevant for Escape Arm outputs.

Missing data after escape because of discontinuation after escape will be imputed accordingly.

For the cohort missing data will be imputed, and summaries will be based on NRI imputed data and on observed case data over time.

Continuous Variables:

- Initial Period

For missing continuous efficacy variables, the last observation carried forward (LOCF) approach will be used. Specifically, missing post-Baseline values will be imputed using the most recent previous value available for a given subject (including Baseline). Only data from scheduled assessments of the parameter at hand will be considered for LOCF.

- Maintenance Period

For missing continuous efficacy variables, the LOCF approach will be used. Only data from scheduled assessments of the parameter at hand will be considered for LOCF. Escapers will be imputed using the value at the time of the escape for all subsequent time points after the escape visit for by blinded maintenance group tables. Observed data after escape is only relevant for Escape Arm outputs.

Missing data after escape because of discontinuation after escape will be imputed accordingly.

For the cohort subjects, missing data will be imputed, and summaries will be based on LOCF imputed data and on observed case data over time.

Safety Variables:

Severity and relationship of AEs should be imputed as severe or related, if missing. Details around imputation of partial dates related to the safety analyses are discussed in Section 3.2.2.

4.3 Interim analyses and data monitoring

An analysis of all available data (including efficacy, safety, PK, and antibodies) will be undertaken after all randomized subjects have completed 24 weeks of placebo-controlled treatment or have withdrawn from the study at the end of the 24-week Double-Blind period. After the Week 24 visit of the final subject, the database will be locked, and a first interim study report will be written. The purpose of this analysis is to perform a comprehensive evaluation of the double-blind efficacy and safety data. The database will be locked, and the actual treatment codes will be made available to UCB personnel (except operational staff working on the study). An interim study report will be written. UCB personnel members will know the allocation information. The investigators and subjects will remain blinded to the assigned treatment after interim data base lock and final data base lock at the completion of the study. Although called an interim analysis, it is a comprehensive double-blind evaluation utilizing all double-blinded data, unblinded listings and all other unblinded variables. A detailed schedule of study assessments is presented in Table 13–1 and a study schematic diagram is presented in Figure 2–1.

A final analysis of all available data will be undertaken after all randomized subjects have completed 52 weeks of treatment or have withdrawn from the study. The purpose of this analysis is to assess maintenance and durability of response as well as longer-term safety risk.

When the study unblinded after the last subject completes the Week 24 Visit and the database is locked for the interim analysis, PS0017 study team members will have access to subject-level randomization data. This operational unblinding to treatment will pertain to preassigned clinical PS0017 study team members but will not extend to blinded staff at the investigational sites. While the blinding of Sponsor clinical study team members is important for ensuring the integrity of data collection and analysis in a controlled study, this unblinding is considered acceptable because the primary evaluation of efficacy at Week 16, upon which sample size calculations were based will be performed in a blinded manner using the Week 24 data.

After the completion of the Week 24 visit of the last subject, an interim database lock will occur, and an interim study report will be written. For subjects completing up to the Week 24 visit, data through Week 24 will be included in the analysis. For subjects withdrawing before Week 24, data through the Safety follow-up visit will be included so long as the follow-up visit does not extend beyond 24 weeks from the first dose of study medication for that subject (ie, what would have been the Week 24 visit). If the Safety follow-up visit extends beyond 24 weeks from the first dose of study medication, data from the Safety follow-up visit will not be included. Safety data from Safety Follow-up visits occurring after the 24-week time point will be captured in the Final Clinical Study Report (CSR). This allows for a maximum treatment period of 24 weeks for each subject in this interim analysis.

No efficacy and safety analysis will be performed for the escape arm in the Interim analyses. Initial period analyses are the same as planned as for the final CSR. The maintenance period analyses will be based on the Blinded Maintenance Set (excluding escapers irrespective of escape visit) for the Interim CSR. The final CSR will contain all efficacy data including escape data as well as SFU data on all patients.

A Data Monitoring Committee (DMC) is not required for the study.

4.4 Multicenter studies

The data from all centers will be pooled for the purposes of the final analyses. There will be no formal statistical evaluation of the effect of center on the results obtained.

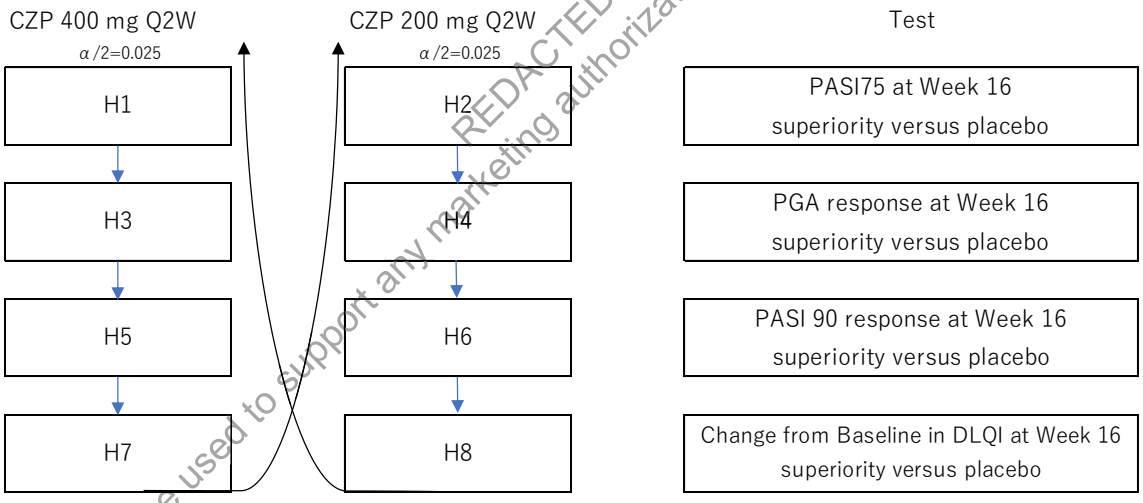
4.5 Multiple comparisons/multiplicity

The statistical analysis of the primary and selected secondary efficacy variables will account for multiplicity and control the familywise type I error rate at a 2-sided alpha level of 0.05 by using a fixed sequence testing procedure. The hypotheses are mapped into 2 sets (H1, H3, H5 and H7) and (H2, H4, H6 and H8) so that hypotheses within each set correspond to the same CZP dose. The type I error will be split equally between CZP 400mg Q2W and CZP 200mg Q2W, so that each dose will be tested at a 2-sided alpha level of 0.025.

The first 2 hypotheses for each dose (H1 for CZP 400mg Q2W; H2 for CZP 200mg Q2W) test whether the given CZP dose is superior to placebo for PASI75 response at Week 16. These are the hypothesis tests corresponding to the primary endpoint. If this is rejected at a 2-sided alpha level of 0.025, that alpha will be passed to the next test in the sequence, allowing the testing procedure to proceed.

The hypotheses associated with the subsequent tests are for secondary efficacy endpoints and are based on testing for superiority relative to placebo. See Figure 4–1 for details on this procedure.

Figure 4–1: Fixed sequence testing procedure



If all hypotheses within one set of hypotheses (either CZP 400mg Q2W or CZP 200mg Q2W) have been rejected, the corresponding type I error probability can be passed on to the other set of hypotheses and that set can be retested if necessary at a 2-sided alpha level of 0.05 (Bretz et al, 2009).

All significance tests are performed at an alpha level of 0.025.

4.6 Use of an efficacy subset of subjects

The FAS is specified as the primary analysis set for efficacy following the intention-to-treat principle. The primary efficacy analysis will be repeated using the PPS, which is a subset of the FAS based on those subjects who completed the Week 16 assessments and do not have any important protocol deviations that would impact the primary efficacy variable.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

Subgroup analyses will be conducted for age, gender, duration of disease, Body Mass Index (BMI), weight, prior systemic chemophototherapy or phototherapy, prior systemic therapy (non-biologic), prior biologic exposure, prior anti-TNF exposure, Baseline PASI score, Baseline PGA score, presence of concomitant PsA at Baseline, presence of Nail psoriasis, treatment emergent anti-drug antibody (TE-ADA) status. These subgroup analyses will be performed on the primary efficacy variable, on PASI90 and PGA response using the FAS and will contain only descriptive statistics for Week 16. The entire subgroup analyses will not be done if at least one subgroup category includes less than 10% of all subjects.

The sub-groups will be defined as follows:

- Age (years): <40, >=40 - <65, >=65
- Gender: Male, Female
- Duration of disease: ≤ median, > median
- BMI: min – 33.3%tile, >33.3%tile – 66.6%tile, >66.6%tile – max
- Weight: min – 33.3%tile, >33.3%tile – 66.6%tile, >66.6%tile – max
- Prior systemic chemophototherapy or phototherapy: yes, no
- Prior systemic therapy (non-biologic): yes, no
- Prior biologic exposure: yes, no
- Prior anti-TNF exposure: yes, no
- Baseline PASI score: min – 33.3%tile, >33.3%tile – 66.6%tile, >66.6%tile – max
- Baseline PGA score: 3, 4
- Presence of concomitant PsA at Baseline: yes, no
- Presence of Nail psoriasis: yes, no
- TE-ADA status: negative, positive (See Section 9.2 for how this is defined in general and for this subgroup analysis).

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number and percentage of screen failures and the primary reason for screen failure will be presented for the ES and CES.

The number of subjects in each analysis set (RS, SS, FAS, PPS, PK-PPS, PsAS and CRS, CSS, CFAS, CPKS, EPS, GPPS) will be presented by investigator, including the dates of the first subject in and the last subject out. The table will be presented overall, by Period (Initial Period and Maintenance Period) and treatment group, for the ES and CES.

Disposition of subjects will be summarized for the RS, PsA Set and CRS by treatment group and overall for the Initial Period. This summary will include the number of subjects that started the period, completed the period, prematurely discontinued study prior to Week 16,

and the reason for discontinuation. A similar summary will be provided for the disposition of subjects in the Maintenance Period by (blinded) maintenance treatment group for the RS and CRS and by escape maintenance treatment group for the Escape Arm on basis of RS.

Subject disposition will be listed for all subjects enrolled and will include the following information: subject status (screen failure, completed or discontinued), date of informed consent, date of randomization, date of first and last dose of study medication (including relative day for last dose, as described in Section 3.2.2), date of premature study termination (if applicable) and primary reason for study termination (if applicable). The listing will also include the date and reason for breaking the randomization code (if applicable) as well as the date of final contact for the subject. For screen failures the date and reason for screen failure will be listed.

5.2 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, on the primary efficacy, key safety, or pharmacokinetic (PK)/pharmacodynamic (PD) outcomes for an individual subject. These important deviations will be identified in blinded data review meetings and will be classified by pre-specified items and summarized by treatment group and overall during the Initial Period for the RS and CRS. Additionally, this table will include a summary of the deviations leading to exclusion from the PPS and PK-PPS.

Important protocol deviations during the Maintenance Period will also be provided by (blinded) maintenance treatment group and by escape maintenance treatment group for the RS and CRS. Since important protocol deviations leading to exclusion from the PPS are only relevant for the Initial Period (as primary efficacy is measured at Week 16), the table of important protocol deviations for the Maintenance Period will not include a summary of important protocol deviations leading to exclusion from the PPS.

All important protocol deviations will be provided in a data listing.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristic variables will be presented for the SS, FAS (plaque PSO), PsAS, PsAS with additional condition to have 3 or more tender and 3 or more swollen joints at Baseline, and for the CSS and CFAS (erythrodermic PSO or generalized pustular PSO). If SS is equal to FAS, only SS is presented.

An additional demographic and other baseline characteristics table will be provided by NRI imputed PASI75 response at Week 16 by randomized treatment group based on FAS.

6.1 Demographics

The following demographic variables will be summarized using descriptive statistics for continuous (mean (SD), median, minimum, and maximum) or categorical (counts and percentages) variables as appropriate:

- Age (years)
- Age class (<40, >=40 - <65, >=65)
- Gender (Female, Male)

6.2 Other Baseline Characteristics

The following Baseline characteristic variables will be summarized using descriptive statistics for continuous (mean (SD), median, minimum, and maximum) or categorical (counts and percentages) variables as appropriate:

- Weight (kg)
- Weight group (min – 33.3%tile, >33.3%tile – 66.6%tile, >66.6%tile – max, see Section 4.8)
- Height (cm)
- BMI (kg/m^2)
- BMI group (min – 33.3%tile, >33.3%tile – 66.6%tile, >66.6%tile – max, see Section 4.8)
- PASI score at Baseline
- PASI score at Baseline: ≤ median, > median
- PASI score at Baseline: min – 33.3%tile, >33.3%tile – 66.6%tile, >66.6%tile – max
- PGA score: 3, 4
- Psoriasis BSA (%)
- Psoriasis BSA at Baseline: ≤ median, > median
- DLQI total score
- Duration of disease (years)

  Duration of disease (years) will be calculated using the date of onset of Psoriasis, erythrodermic pustular Psoriasis or generalized pustular Psoriasis as follows:

  Duration of disease (years) = (Date of Randomization - Date of onset of Psoriasis)/365.25

  Note: If the date of onset of psoriasis 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).

  If the imputed date results in a subject having a disease duration of less than six months and the inclusion criterion related to having PSO for at least six months is confirmed to not have been violated, then the subject's duration of disease will be set to 6 months. If that criterion has been violated, then the subject's duration of disease will be the imputed value of less than 6 months.

  If the imputed date results in a subject having a negative disease duration (because the imputed date of onset is after date of randomization), then the date of onset will be set to date of given informed consent.
- Duration of disease (years): ≤ median, > median
- Previous biologic therapy: never used, used: (1 therapy, 2 therapies, >=3 therapies)
- Previous systemic non-biologic therapy: never used, used: (1 therapy, 2 therapies, >=3 therapies)
- Prior chemophototherapy or phototherapy: yes, no
- Any systemic treatment for PSO: yes, no

A subject will be classified as receiving prior systemic therapy for psoriasis if they ever received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic chemophototherapy or phototherapy. Subjects who never received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic chemophototherapy or phototherapy will be classified as not receiving prior systemic treatment for psoriasis.

- Prior systemic treatment for PsA (only PsAS): yes, no

  A subject will be classified as receiving prior systemic treatment for PsA if the ever received prior medications with PsA indication. Exclude any medications that are applications. Everything remaining after this step should be considered a systemic treatment for PsA.

- Prior anti-TNF therapy used: yes, no
- Prior exposure to at least 2 systemic treatments out of phototherapy, methotrexate, and cyclosporine (with no previous biologic exposure): yes, no
- Itch Numeric Rating Scale at Baseline
- PhGADA (only PsAS)
- PGADA (only PsAS)
- PGAAP (only PsAS)
- Tender joint count (only PsAS)
- Swollen joint count (only PsAS)
- HAQ-DI (only PsAS)
- CRP (mg/L) (only PsAS)
- DAS28 (CRP) (only PsAS)
- DAS28 (CRP) (only PsAS): <2.6 (remission), >=2.6 to <= 3.2 (low disease activity), >3.2 to <=5.1 (middle disease activity), and >5.1 (high disease activity)
- JDA score (only GPPS)

Furthermore, psoriasis Baseline characteristics will be tabulated:

- Presence of concomitant PsA at Baseline: yes, no

  The presence of concomitant PsA at Baseline will be based on data queried directly in eCRF.

- Presence of Nail psoriasis: yes, no

6.3 Medical history and concomitant diseases

Previous and ongoing medical history conditions will be summarized by MedDRA® system organ class (SOC) and preferred term (PT) using the SS and the CSS. Medical procedures are not coded and will only be presented in listings. Medical history will be summarized using descriptive statistics for categorical data and for continuous data (duration of psoriasis).

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of study medication. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For CZP or PBO, the dosing period is from the date of first dose up to (but not including) 14 days post last dose. Thus, in general, a concomitant medication is any medication that was taken on or after the date of first study medication and prior to the date of last study medication administration + 14 days. Medications that started prior to the start date of study medication and ongoing after the start date of study medication will be both prior and concomitant.

Prior as well as concomitant psoriasis medications will be summarized by randomized treatment group and overall based on the SS and CSS. This summary will be based on the eCRF page for psoriasis treatment history.

The following rules are applied to impute partial start and stop dates for concomitant medications.

Imputation of Partial Start Dates:

If only the month and year are specified and the month and year of first dose 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 first dose is the same as the month and year of the start, then use the date of first dose.

If only the year is specified, and the year of first dose 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 first dose is the same as the year of the start date, then use the date of first dose.

If the start date is completely unknown, and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.

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 stop date is completely unknown, do not impute the stop date.

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.

Medications will be summarized by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and Preferred Term.

Concomitant medications will be summarized for the Initial Period and for the Maintenance Period based on the SS and CSS. For subjects who complete the Initial Period through Week 16, the relevant period for counting concomitant medications is from Baseline to Week 16 (inclusive). If a subject discontinues prior to Week 16, then the general definition described at the beginning of this section will apply. For the summary of concomitant medication in the Maintenance Period, the general definition of concomitant medication provided at the beginning of this section will apply, where the date of first dose is the dose at Week 16.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance will utilize the number of administered injections and compare them to the scheduled expected number of injections. The sum of difference in number of injections between the actual and the expected injections will be summarized. In addition, the percent compliance will be calculated as:

Compliance (%) = 100 x (number of injections received / number of injections expected)

and summarized using descriptive statistics for continuous data for the SS, FAS, CSS, and CFAS. Additionally, compliance will be summarized categorically based on whether subjects have compliance <80% or ≥80%.

The sum will be calculated for every visit of the considered period. Analyses according to the second approach will also be done for the SS, FAS, CSS, and CFAS.

The following compliance summaries will be performed:

- Initial Period – The first dose of the Initial Period is the first study dose at Baseline (Week 0) and the intended last dose is the Week 14 dose.
- Maintenance Period – The first dose of the Maintenance Period is the Week 16 dose and the intended last dose is the Week 50 dose. For the Interim Analysis, the intended last dose is the Week 22 dose.
- Combined Initial and Maintenance Period – The first dose of the Combined Initial and Maintenance Period is the first study dose at Baseline (Week 0) and the intended last dose is the Week 50 dose. For the Interim Analysis, the intended last dose is the Week 22 dose.

For visits where a subject is expected to receive study medication, see Table 13–1. If a subject withdrew at a visit in which they were supposed to receive study treatment, then it will not be expected that the subject received an injection at that visit. In the case that a subject is lost to follow-up, and an early discontinuation visit is not conducted, then administration on last visit where the subject was available will be considered in the calculation of compliance.

8 EFFICACY ANALYSES

Because the majority of PBO subjects will be switched to CZP treatment at or after Week 16, all statistical comparisons between CZP and PBO will be limited to the time period through Week 16 for subjects with moderate to severe chronic plaque PSO. After Week 16, data will be summarized using descriptive statistics only.

8.1 Statistical analysis of the primary efficacy variable(s)

8.1.1 Derivations of primary efficacy variable(s)

The primary efficacy variable for subjects with moderate to severe chronic plaque PSO is the PASI75 at Week 16. The PASI is the most commonly used and validated assessment for grading the severity and extent of the disease.

The PASI score is calculated as follows:

The percent area of involvement (BSA%) is estimated across 4 body areas: head (h) (10% of a person's skin), arms (a) (20%), trunk (t) (30%), legs (l) (40%).

For each section, the percent of area of skin affected (A), is estimated and then transformed into a grade from 0 to 6:

- Grade 0 none
- Grade 1: <10% of involved area affected
- Grade 2: 10% to <30% of involved area affected
- Grade 3: 30% to <50% of involved area affected
- Grade 4: 50% to <70% of involved area affected
- Grade 5: 70% to <90% of involved area affected
- Grade 6: 90% to 100% of involved area affected

Within each section, the severity is estimated by 3 clinical signs: redness (R), thickness (T) and scaling (S). Severity is measured on a scale from 0 to 4 (0 = none and 4 = very marked).

The PASI is a measure of the average redness, thickness, and scaling of the psoriatic skin lesions, multiplied by the involved psoriasis area score of the respective section, and weighted by the percentage of the person's affected skin for the respective section. The following formula is used to calculate the PASI:

PASI = 0.1 x (Rh+Th+Sh) x Ah+ 0.2 x (Ra+Ta+Sa) x Aa + 0.3 x (Rt+Tt+St) x At
+ 0.4 x (Rl+Tl+Sl) x Al

The PASI ranges from 0 to 72 with a higher score indicating increased disease.

If a subject is missing 1 or 2 severity measurements for a certain region, the average of the remaining severity measurement(s) within that region will be utilized to substitute for the missing severity measurement(s) in that region. If the area of affected skin and/or all severity measurements for up to 2 regions are missing, then the missing (R+T+S) x A for a region will be substituted by the average of the available (R+T+S) x A. Otherwise, the PASI will be set to missing.

The PASI75 response is based on at least 75% improvement from Baseline in the PASI score.

The % improvement in PASI scores from Baseline will be computed as:

$$\%\ \text{improvement from Baseline} = 100 \times (\text{Baseline PASI} - \text{Observed PASI}) / (\text{Baseline PASI})$$

If a subject has experienced an improvement, this measure will be positive. If a subject has experienced a worsening in their condition, this measure will be negative.

The categorical variable PASI75 is defined to be equal to 1 for % improvement from Baseline in PASI scores of 75% or greater and 0 for less than 75%. The classification of subjects as responder or non-responder is based on this definition: 1 = responder, 0 = non-responder.

Similarly, the PASI50, PASI75, PASI90 and PASI100 responses are equal to 1 for subjects with at least 50%, 75%, 90%, and 100% improvement.

8.1.2 Primary analysis of the primary efficacy variable

The primary analysis for the PASI75 response at Week 16 will be based on a logistic regression model for the FAS which will include fixed effects for treatment group and prior biologic exposure (yes/no). Prior biologic exposure was selected as a fixed effect in the logistic regression model as it is a stratification variable for randomization and because it may have an impact on efficacy. The odds ratio, associated confidence interval, and p-value

will be presented. If convergence is not obtained due to having only or no responders in one or more treatment groups, then an exact logistic regression will be applied and odds ratio, associated exact confidence interval, and exact p-value will be determined. If the logistic regression model is unable to converge, then prior biologic exposure may be dropped from the model to facilitate convergence. This model is used when the sample size is too small for a regular logistic regression or when some of the cells formed by the outcome and categorical predictor variable have no observation.

The Markov Chain Monte Carlo (MCMC) method for multiple imputation will be used to account for missing values in the primary analysis of PASI75 at Week 16. The multiple imputation procedure for PASI75 will be based on the actual PASI score.

For derivation of PASI75 response, no rounding will be performed. That is, the imputed Week 16 PASI value will be compared directly to the observed Baseline value to determine whether or not a reduction of at least 75% was achieved.

Each CZP dose will be compared against PBO to establish superiority over PBO and will be tested sequentially at an alpha of 0.025 as outlined in Section 4.5.

Multiple imputation and the subsequent analysis will involve the 3 tasks described below:

1. Create a data set, one for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing PASI values in each data set will be filled in using the MCMC method with a total of 75 sets of imputation being performed. The seed used for these imputations will be 958 (Note: All other multiple imputation procedures described in this SAP will use this same seed as well). The procedure will sequentially estimate an imputation model for the PASI score at each post-Baseline visit (up to Week 16) where PASI is collected, with prior biologic exposure, and Baseline score as predictors. Note that PASI scores at earlier visits will also be used as predictors for the model of PASI at later visits. The resulting data sets for each treatment arm will be combined into one complete data set based on each of the 75 imputations.

   Note: If one treatment group is complete, so without any missing values, then this treatment group is excluded from MCMC imputation and the observed data will be duplicated 75 times and rejoined to the imputed data set.

   Note: The imputation model based on the MCMC method will only allow continuous variables as predictors. Therefore, prior biologic exposure will be re-coded as indicator variables (with values of 0 or 1). Because prior biologic exposure has just 2 levels, only one indicator variable will be needed.

2. For each complete imputed data set, the dichotomous responder rate based on the PASI scores will be computed. Each complete imputed data set will then be analyzed based on a logistic regression model with factors of treatment group and prior biologic exposure (yes/no).

   Note: For derivation of PASI75 response, the imputed PASI value will be compared directly to the observed Baseline PASI value to determine whether or not a reduction of at least 75% was achieved. If values outside of the pre-defined range of values for PASI (0-72) are imputed, they will be cut off as appropriate after the multiple imputation procedure but before deriving the responder variables. For example an imputed PASI value of -0.5 would be changed to 0 before deriving the PASI75 responder variable.

3. The Week 16 results from the logistic regression analysis of each of the 75 imputed data sets will be combined into a single inference using SAS PROC MIANALYZE.

Some key points to consider relative to the calculation of the odds ratios and corresponding confidence intervals are noted below:

As the estimates of the odds ratios from the logistic regression model follow a log-normal distribution, a log transformation is needed to normalize these estimates since the procedures for combining results from multiple imputed datasets are based on the assumption that the statistics estimated from each imputed dataset are normally distributed. Therefore, the log of the odds ratio estimates from the logistic regression model will need to be used when combining into a single inference (the PROC MIANALYZE step). Additionally, the standard errors for the odds ratios are transformed as follows:

$$[\log(UCL) - \log(LCL)] / (2*Z_{\alpha/2})$$

where UCL and LCL are the upper and lower confidence limit, respectively, for the confidence interval of the odds ratio from the logistic regression model, and $Z_{\alpha/2}$ is the relevant critical value from the standard normal distribution (based on α=0.05 for a 95% confidence interval and α=0.025 for a 97.5% confidence interval).

The PROC MIANALYZE step takes the estimates of the log odds ratio and standard errors for each imputation and combines them to derive a single estimate of the log odds ratio and corresponding standard error. The odds ratio is then estimated by exponentiating the estimate of the log odds ratio. The confidence limits of the odds ratio are then estimated as follows:

$$LCL = OR*\exp(-SE*Z_{\alpha/2})$$

$$UCL = OR*\exp(SE*Z_{\alpha/2})$$

where OR is the back-transformed estimate of the odds ratio just described, SE is the standard error of the log odds ratio derived in PROC MIANALYZE, and $Z_{\alpha/2}$ is the relevant critical value from the standard normal distribution (based on α=0.05 for a 95% confidence interval and α=0.025 for a 97.5% confidence interval). These calculations will be done such that odds ratios and corresponding confidence intervals are calculated for the odds ratio of each CZP dose versus placebo. Note that the p-values presented in the tables will be the ones provided initially by PROC MIANALYZE and are not impacted by the transformations described above.

In addition to calculating the odds ratio, associated CIs, and p-values for the pairwise comparisons of each CZP treatment group with PBO, the estimated proportion of responders (eg, estimated responder rate) and the difference in the proportion of responders between each CZP treatment group and PBO will be estimated, and 2-sided 95% CIs will be created for each difference. The creation of these estimates will be completed for each CZP treatment group using the process detailed below:

1. Use the logistic regression model to calculate:

a. Least squares mean estimates of the log odds of CZP (G_C) and PBO (G_P), as well as their corresponding standard errors (S_C and S_P, respectively)

b. Standard error of the least squares mean estimate of the log odds ratio (S_R)

2. Compute estimates for predicted proportions using the following transformations:

$P_C = \exp(G_C)/(1 + \exp(G_C))$

$P_P = \exp(G_P)/(1 + \exp(G_P))$

The difference in proportions is then given by:

$D = PC - PP$

3. Estimate the standard error of D by:

$$S_D = \text{sqrt}[\ P_C^2\ (1 - P_C)^2\ S_C^2 + P_P^2\ (1 - P_P)^2\ S_P^2 + P_C\ (1 - P_C)\ P_P\ (1 - P_P)\ S_R^2 - P_C\ (1 - P_C)\ P_P\ (1 - P_P)\ (S_C^2 + S_P^2)]$$

The Markov Chain Monte Carlo (MCMC) method for multiple imputation, as previously outlined, will be used to account for missing values of PASI. This method will create multiple complete data sets which may be analyzed with the process described above. An estimate for the difference in proportions, D, and corresponding standard error, SD, will be computed for each complete dataset.

The results from these analyses will be combined into a single 2-sided 95% confidence interval using SAS PROC MIANALYZE.

In cases where one treatment group has either no responders or only responders, exact logistic regression will be used to calculate the odds ratio with its corresponding confidence interval and p-value. The exact logistic regression will include treatment, and prior biologic exposure as in the primary model. The following procedure will be used to obtain these estimates:

1. Obtain the odds ratio and lower 2-sided confidence limit (based on α=0.05 for a 95% confidence interval and α=0.025 for a 97.5% confidence interval) for each imputation from PROC LOGISTIC using the EXACT statement and ESTIMATE=BOTH option.
2. Take the log of the exact odds ratio for each imputation and calculate [log(odds ratio) - log(lower/upper CL)]/ $Z_{\alpha/2}$ for each imputation as the standard error. Note the upper/lower CL will not be used as it is undefined for cases where there are no/only responders in a treatment group.
3. Use PROC MIANALYZE to combine the log odds ratio estimates and standard errors into a single estimate and corresponding standard error.
4. Exponentiate the estimate obtained from the previous step to obtain the odds ratio and calculate the confidence interval as OR*exp+/-(SE*$Z_{\alpha/2}$) where OR is the odds ratio estimate and SE is the combined estimate of the log odds ratio from PROC MIANALYZE.

This method of exact logistic regression will be used for any endpoint in the statistical hierarchy when one treatment group has no responders.

The calculation of responder rates and the differences in proportion of responders is also impacted when at least one treatment group has no/only responders. In this case, the responder rate will be calculated as the simple proportion of responders for each treatment group across all 75 imputed data sets. The difference in proportions between each CZP group and placebo is calculated for each imputation. The standard error of the difference in proportions for a given CZP group versus placebo is then calculated for each imputation. The standard error is calculated as:

$$\sqrt{\hat{p}(1-\hat{p})(\frac{1}{n_1}+\frac{1}{n_2})},$$

where

$$\hat{p} = \frac{Y_1 + Y_2}{n_1 + n_2}.$$

Note that Y_1 and Y_2 are the number of responders in the placebo and given CZP group, respectively, while n_1 and n_2 are the total number of subjects in each group, respectively. The estimates for the difference in proportion of responders and the standard error above are passed into PROC MIANALYZE so that the overall difference in proportion of responders and the 95% confidence interval can be calculated.

Some additional considerations in the event that there are no/only responders in a given treatment group are as follows:

- If there are no/only observed responders in any treatment group, then none of the calculations described above will be done and the responder rates will be presented as 0/1 while all other statistics will not be calculated.
- If there are no/only observed responders in two of the groups, then responder rates will be calculated as described above, but the difference in proportions and odds ratio calculations will be done only for PBO and the CZP group with more than 0 responders.
- If there is a case where all imputed data sets are exactly the same, then combined estimates of the standard error cannot be calculated. Therefore, the results will be based on the actual observed data and on the (exact) logistic regression using this data.

8.1.3 Supportive and sensitivity analyses of the primary efficacy variables

Analyses will be performed to evaluate the sensitivity of the efficacy results to the method for handling missing data and the statistical analysis method. The following sensitivity analysis will be performed on the primary variable: Non-responder imputation (NRI) will be performed to impute missing values. Specifically, any subject with a missing PASI75 value at Week 16 will be treated as a non-responder for analysis purposes. The logistic regression model will be used on the imputed data as outlined in Section 8.1.2. Additionally, responder rates will be determined for the observed results.

The PPS will also be used for a sensitivity analysis of the primary endpoint. The same methods as outlined in Section 8.1.2 will be used. If there are no missing data for the primary efficacy endpoint in the PPS, then no imputation will be performed, and the logistic regression model will be used on the observed data.

Subgroup analyses will be conducted for age, gender, duration of disease, BMI, weight, prior systemic chemotherapy or phototherapy, prior systemic therapy (nonbiologic), prior biologic exposure, prior anti-TNF exposure, Baseline PASI score, Baseline PGA score, presence of concomitant PsA at Baseline, presence of Nail psoriasis, and TE-ADA status. These subgroup analyses will contain descriptive statistics for the FAS at Week 16 using both the NRI and the observed case (OC) data. The entire subgroup analyses will not be done if at least one subgroup category includes less than 10% of all subjects.

For subjects with erythrodermic PSO or generalized pustular PSO, no primary efficacy variable(s) are planned.

8.2 Statistical analysis of the secondary efficacy variables

The secondary efficacy variables will be analyzed for all subjects in the FAS.

Secondary efficacy variables are PASI90, PGA response, and change from Baseline in DLQI and Itch Numeric Rating Scale at Week 16. For subjects with erythrodermic PSO or generalized pustular PSO, no secondary efficacy variables are planned.

Beside the analyses described in the following sections, tables with descriptive statistics will be provided for the secondary efficacy variables by randomized treatment group for the Initial Period.

Subgroup analyses will be conducted for age, gender, duration of disease, BMI, weight, prior systemic chemotherapy or phototherapy, prior systemic therapy (nonbiologic), prior biologic exposure, prior anti-TNF exposure, Baseline PASI score, Baseline PGA score, presence of concomitant PsA at Baseline, presence of Nail psoriasis, and TE-ADA status. These subgroup analyses will only be performed on PASI90 and PGA response using the FAS and will contain only descriptive statistics for Week 16 using both the NRI and the observed case (OC) data. The entire subgroup analyses will not be done if at least one subgroup category includes less than 10% of all subjects.

8.2.1 Physician's Global Assessment (PGA) Clear or Almost Clear (with at least 2 category improvement) at Week 16

A static PGA for PSO will be used to assess disease severity in all subjects during the trial. The Investigator will assess the overall severity of PSO using the 5-point scale detailed in Table 8–1.

Table 8–1: Physician's Global Assessment

Score	Short Descriptor	Definition
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep red dark coloration; severe/coarse scaling covering almost all or all lesions

A subject will be classified as a responder at Week 16 if they achieve a PGA score of 0 ('Clear') or 1 ('Almost clear') and they have at least a 2-category improvement relative to Baseline. Note that a PGA score of at least 3 is required per the inclusion criteria, so all subjects achieving a PGA score of 0 or 1 should, by definition, be a responder. However, in the case that a subject with a Baseline score of 2 is mistakenly randomized, then this subject may be classified as a responder only if a PGA score of 0 is achieved (thereby achieving the required 2-category improvement).

PGA response at Week 16 will be analyzed for treatment effects using pairwise comparisons based on the same method as that for the primary efficacy variable.

The MCMC algorithm is based on the multivariate normal model; imputed values for PGA will not generally be one of the discrete values actually used in PGA scoring (0, 1, 2, 3, or 4). Therefore, standard rounding rules will be applied to the imputed values in order to derive the

binary PGA response variable. For example, if a subject has a PGA score imputed as 1.4 (and assuming a Baseline PGA score of 3), this imputed value would be rounded down to 1, and the minimum change from Baseline of 2 would have been met. Therefore, this subject would be considered a responder.

The significance testing of each CZP treatment group vs PBO will be part of the fixed sequential testing procedure described in Section 4.5.

8.2.2 PASI90 at Week 16

PASI90 response at Week 16 will be analyzed for treatment effects using pairwise comparisons based on the same method as that for the primary efficacy variable. Each CZP dose will be compared against placebo to establish superiority over placebo and will be tested at a significance level of 0.025 as part of the fixed sequence testing procedure outlined in Section 4.5.

8.2.3 Change from Baseline in DLQI at Week 16

The Dermatology Life Quality Index (DLQI) is a skin-disease-specific questionnaire evaluating how symptoms and treatment affect patients' Health-Related Quality of Live (HRQoL). This instrument includes 10-questions that cover 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment, as assessed over the past week. It is validated and reproducible in PSO patients.

The scoring of each answer for the DLQI is as follows:

Table 8–2: DLQI scoring

Response	Score
Very much	3
A lot	2
A little	1
Not at all	0
Not relevant	0
Question unanswered	0
Q7: 'prevented work or studying' = yes	3

The DLQI is calculated by adding the score of each question and ranges from 0 to 30 with higher scores indicating lower HRQoL:

Meaning of DLQI Scores

0-1 = no effect at all on patient's life

2-5 = small effect on patient's life

6-10 = moderate effect on patient's life

11-20 = very large effect on patient's life

21-30 = extremely large effect on patient's life

A ≥4-point change in the DLQI score (DLQI response) has been reported to be meaningful for the patient (within-patient minimal important difference); a DLQI absolute score of ≤1

indicates DLQI remission (ie, no or small impact of the disease on HRQoL) (Basra et al, 2015).

Because Question 7 (Q7) has a sub-question (referred to as Q7a here) after the leading yes/no question, some clarifying rules for scoring are provided:

- If Q7='yes', then score=3 regardless of the responses to Q7a.
- If Q7='no', 'not relevant', or is missing and Q7a='A lot', then score= 2.
- If Q7='no', 'not relevant', or is missing and Q7a='A little', then score=1.
- If Q7='no', 'not relevant', or is missing and Q7a='Not at all', then score=0.
- If Q7='no', 'not relevant', and Q7a is missing or not applicable, then score=0.
- If Q7 is missing and Q7a is missing, Q7 is considered unanswered (see below for details on how this impacts the overall DLQI score).

If 1 question is left unanswered, this is scored 0 and the scores are summed as usual. If 2 or more questions are left unanswered, the questionnaire is not scored.

The analysis of DLQI will be based on the change from Baseline at Week 16 for the FAS. Treatment group comparisons for each CZP treatment group vs placebo will be performed using an analysis of covariance (ANCOVA) model with treatment group and prior biologic exposure as factors and Baseline DLQI score as a covariate. The least squares (LS) means and standard errors derived from the model will be presented for each treatment group. Additionally, adjusted mean treatment differences, corresponding confidence intervals, and p-values will be reported. Missing values will be imputed using LOCF. Each CZP dose will be compared against placebo to establish superiority over placebo and will be tested at a significance level of 0.025 as part of the fixed sequence testing procedure outlined in Section 4.5.

8.2.4 Change from Baseline in Itch Numeric Rating Scale at Week 16

The Itch Numeric Rating Scale has been developed as a simple, single item instrument to assess the patient-reported severity of itch at its greatest intensity during the past 24h period. Subjects indicate itch severity by circling the integer that best describes the worst level of itching due to PSO in the past 24h period on an 11-point scale anchored at 0, representing "no itching" and 10, representing "worst itch imaginable" (Kimball et al, 2016).

Descriptive statistics for observed and change from baseline in Itch Numeric Rating Scale at Week 16 values will be presented for the FAS. Treatment group comparisons for each CZP treatment group vs placebo will be performed using an analysis of covariance (ANCOVA) model with treatment group and prior biologic exposure as factors and Baseline Itch Numeric Rating scale as a covariate. The least squares (LS) means and standard errors derived from the model will be presented for each treatment group. Additionally, adjusted mean treatment differences, corresponding 95% confidence intervals, and p-values will be reported. Missing values will be imputed using LOCF.

8.3 Analysis of other efficacy variables

A combination of both inferential and descriptive statistics will be used to analyze data collected up to Week 16 for the other efficacy variables. No adjustment for multiplicity will be made. After Week 16, data will generally be summarized using descriptive statistics only, unless otherwise specified. The general rules for which treatment groups will be used to

summarize data and how missing data will be handled across study periods are outlined in Section 3.6 and Section 4.2. Any exceptions are noted in the relevant section below.

Table 8–3 presents an overview of the analysis of other efficacy variables.

Table 8–3: Overview of analysis of other efficacy variables

Population	Other efficacy variable	Analysis Set
Double-Blind Overall, Escape Arm, Cohort erythrodermic PSO	PASI50, PASI75, PASI90, and PASI100	FAS, EPS
	PGA clear or almost clear (with at least 2-category improvement)	
	Absolute and percent change from Baseline in PASI score	
	PGA score distribution	
	Absolute and percent change from Baseline in the BSA affected by PSO	
Double-Blind Overall	Time to onset of action, defined as the time to PASI50	FAS
	Time to onset of action, defined as the time to PASI75	
	Time to onset of action, defined as the time to PASI90	
	Time to onset of action, defined as the time to PASI100	
Double-Blind Overall, Escape Arm, Cohort Overall	Change from Baseline in DLQI mean scores, percent of subjects achieving MCID, and percent achieving DLQI remission	FAS, CFAS
Double-Blind Overall, Escape Arm, Cohort Overall	Change from Baseline in Itch Numeric Rating Scale mean scores and percent of subjects achieving MCID	FAS, CFAS
Double-Blind PsA, Escape Arm	ACR20, 50, 70 and change from Baseline in all individual ACR core components in the subpopulation of subjects with PsA at Baseline	PsAS
	Change from Baseline in DAS28(CRP) and CRP (mg/L)	
Double-Blind NAPSI, Escape Arm	Change from Baseline in mNAPSI in the subpopulation of subjects with nail disease at Baseline	NAPSIS
Cohort overall	Clinical Global Impressions of Improvement (CGI-I)	CFAS
Cohort generalized pustular PSO	Global Improvement Score	GPPS
	Japanese Dermatological Association (JDA) severity index	

Table 8–4: Overview of analysis of variables in interim analysis

Population	Variable	Period	Analysis Set
Disposition and important protocol deviations as planned for final CSR			
Demographic and baseline characteristics as planned for final CSR			
Primary and secondary efficacy variables as planned for final CSR			
Other efficacy variables			
Double-Blind Overall, Cohort erythrodermic PSO	PASI50, PASI75, PASI90, and PASI100	Initial and Maintenance*	FAS, EPS
	PGA clear or almost clear (with at least 2-category improvement)		
	Absolute and percent change from Baseline in PASI score		
	PGA score distribution		
	Absolute and percent change from Baseline in the BSA affected by PSO		
Double-Blind Overall	Time to onset of action, defined as the time to PASI50	Initial	FAS
Double-Blind Overall, Cohort Overall	Change from Baseline in DLQI mean scores, percent of subjects achieving MCID, and percent achieving DLQI remission	Initial and Maintenance*	FAS, CFAS
	Change from Baseline in Itch Numeric Rating Scale mean scores and percent of subjects achieving MCID		
Double-Blind PsA	ACR20, 50, 70 and change from Baseline in all individual ACR core components in the subpopulation of subjects with PsA at Baseline	Initial and Maintenance*	PsAS
	Change from Baseline in DAS28(CRP) and CRP (mg/DL)		
Double-Blind NAPSI	Change from Baseline in mNAPSI in the subpopulation of subjects with nail disease at Baseline	Initial and Maintenance*	NAPSIS
Cohort overall	Clinical Global Impressions of Improvement (CGI-I)	Initial and Maintenance*	CFAS

Table 8–4: Overview of analysis of variables in interim analysis

Population	Variable	Period	Analysis Set
Cohort generalized pustular PSO	Global Improvement Score	Initial and Maintenance*	GPPS
	Japanese Dermatological Association (JDA) severity index score		
PK/PD variables as planned for final CSR			
Safety variables as planned for final CSR			

*: Maintenance Period carried out at Week 24 instead of Week 52 as in the final analysis.

8.3.1 PASI50, PASI75, PASI90, and PASI100 by Visit

See Section 8.1.1 for details of the derivation.

Initial Period

PASI50, PASI75, PASI90 and PASI100 responder rates will be summarized by randomized treatment group for the FAS at each time point (Weeks 2, 4, 8, 12 and 16). A comparison between treatment groups will be made at each time point using the same model and approach for handling missing data as described for the primary analysis. The estimate for the responder rate, the odds ratio, 95% CI, and p-value from the model will be presented. Additionally, the responder rates based on the observed data will be summarized using counts and percentages. Each time point will be analyzed separately. If the model fails, percentages for the responders and the corresponding 95% CIs will be displayed. If convergence is not obtained due to lack of responders in one or more treatment groups, methods described in Section 8.1.2 will be applied instead. For EPS only descriptive statistics will be provided.

Line plots will be generated to present PASI50, PASI75, PASI90 and PASI100 responder rates (as derived by the above procedure) by randomized treatment group through Week 16.

Blinded Maintenance Period (Interim Analysis, excluding subjects who escaped at Week 16)

The summaries will include the observed responder rates at each visit. Subjects who meet the criterion for escape (ie, not achieving PASI50 response) at Week 16 are excluded from the point of escape.

For other missing data, multiple imputation will be performed based on MCMC methodology. The analysis (logistic regression) of response rate on MCMC imputed data is similar to the procedure outlined in Section 8.1.2 except that escape subjects are not considered here. The estimated responder rates and corresponding 95% confidence intervals for the difference in proportion of responder vs. PBO and odds ratios vs PBO with 95% confidence interval and p-value at each visit will be presented by blinded maintenance treatment group based on the FAS.

Additionally, NRI will be used for imputation of missing data. The estimated responder rates, odds ratios vs PBO with corresponding 95% confidence interval and p-value at each visit in

the Blinded Maintenance Period [ie, Week 16 through Week 24] will be presented by blinded maintenance treatment group based on the FAS.

PASI50, PASI75, PASI90 and PASI100 responder rates (based on simple counts and percentages only) will be also summarized for the Blinded Maintenance Period (Week 16 through Week 24) by blinded maintenance treatment group (combined group inclusive) using NRI imputed and observed data.

A table summarizing the (exact) logistic regression analysis results of PASI75/PASI90 response rates during Blinded Maintenance Period based on the subset of PASI75/PASI90 responders at Week 16 will also be provided (observed case, NRI and MCMC imputed data), procedure as outlined in Section 8.1.2. Additionally, the same table will be produced to summarize simple counts and percentages using the blinded maintenance treatment groups (combined group inclusive) based on NRI and observed data only.

Line plots will be generated to present the percentages of responders over time by blinded maintenance treatment group (Blinded Maintenance Period treatment) over time (from Week 16 to Week 24) based on MCMC imputed data.

Maintenance Period (Final Analysis, including subjects who escaped after Week 16)

The analysis of the PASI50, PASI75, PASI90, and PASI100 responder rate during the Maintenance Period will be based on the BM FAS. Missing data will be handled based on a combination of NRI and multiple imputation. The procedure is described below:

1. Identify subjects who met the escape criterion at any timepoint (ie, did not achieve a PASI50 response), and do not include them in the multiple imputation model described in Step 2.
2. For all subjects not identified in Step 1, create a data set, one for each treatment group, of subjects with observed values and those needing estimation by multiple imputation. The missing PASI values in each data set will be filled in using the MCMC method with a total of 75 sets of imputations being performed. The procedure will sequentially estimate an imputation model for the PASI score at each post-Baseline visit where PASI is collected, with prior biologic exposure and Baseline score as predictors. The resulting data sets for each treatment arm will be combined into one complete data set based on each of the 75 imputations.
3. For the subjects meeting the escape criterion identified in Step 1, all visits after the point of escape will be imputed via NRI. This imputation is based on meeting the escape criterion, whether or not the subject actually received escape treatment. Once imputation has been performed for these subjects, these records are duplicated 75 times and combined with the 75 imputations performed in Step 2.

   Note: If subjects identified here have intermittent missing data at earlier time points, those will be imputed via NRI.
4. For each complete imputed data set, the dichotomous PASI responder rate based on the PASI scores will be computed. Each complete imputed data set will then be analyzed using simple proportions by treatment group (p=x/N, where x is the number of responder and N the number of subjects in this treatment group). The corresponding standard error for the sample proportion will be calculated with the square root of p(1-p)/N.

   Note: For derivation of PASI75 response, the imputed PASI value will be compared directly to the observed Baseline PASI value to determine whether or not a reduction of at least 50% (or 75%, 90%, 100%) was achieved. If values outside of the pre-defined range

of values for PASI (0-72) are imputed, they will be cut off as appropriate after the multiple imputation procedure but before deriving the responder variables. For example, an imputed PASI value of -0.5 would be changed to 0 before deriving the PASI responder variable.

5. The results at each week of each of the 75 imputed data sets will be combined into a single inference using SAS PROC MIANALYZE.

The estimated responder rates at each week will be presented by treatment group based on the FAS.

Additionally, NRI will be used for imputation of missing data. Simple proportions will be calculated to estimate responder rates at each visit in the Maintenance Period (ie, Week 16 through Week 52). Responder rates based on observed case data will also be summarized.

A table summarizing the PASI75/PASI90 response rates (simple proportions) during Maintenance Period based on the subset of PASI75/PASI90 responders at Week 16 will also be provided (observed case, NRI and MCMC imputed data).

Line plots will be generated to present the percentages of responders over time by maintenance treatment group over time (from Week 16 to Week 52) based on MCMC imputed data.

Escape Arm in Maintenance Period (Final Analysis, including data after escape for subjects who escaped at/after Week 16)

Observed PASI50, PASI75, PASI90 and PASI100 responder rates will be summarized by the treatment group before escape from Week 16 to Week 52 based on EM FAS. Observed results in maintenance period but before escape will not be included in this table.

Additionally, the observed PASI50, PASI75, PASI90 and PASI100 responder rates will be summarized by the treatment group before escape and by escape maintenance treatment group from Week 16 to Week 52 based on EM FAS. Due to up-titration, subjects may be presented in both escape maintenance treatment groups (Esc CZP 200mg Q2W, Esc CZP 400mg Q2W), so that the sum of the sample sizes of both treatment groups will exceed the number of escapers.

Combined Initial and Maintenance Period (Interim Analysis, excluding subjects who escaped at Week 16)

PASI50, PASI75, PASI90 and PASI100 responder rates will be summarized by randomized treatment group at each visit from Week 0 to Week 24 based on NRI and observed case data. Responder rates based on NRI data, odds ratios with corresponding 95% CIs will be derived without modelling but only by calculating counts, percentages and CIs. No p-values will be presented. For the NRI summary, subjects will be imputed as non-responders at the point of escape or for those subjects who do not escape, from the point of premature withdrawal through Week 24. For observed data, no imputation will be performed and counts and percentages of responders will be presented.

Combined Initial and Maintenance Period (Final Analysis, including subjects who escaped at/after Week 16)

PASI50, PASI75, PASI90 and PASI100 responder rates will be summarized by randomized treatment group at each visit from Week 0 to Week 52 based on NRI and observed case data. Responder rates based on NRI data will be derived without modelling but only by calculating counts and percentages. No p-values will be presented. For the NRI summary, subjects will

be imputed as non-responders at the point of escape or for those subjects who do not escape, from the point of premature withdrawal through Week 52. For observed data, no imputation will be performed and counts and percentages of responders will be presented.

Additionally, the same table will be produced at each visit from Week 0 to Week 52 based on FAS by the following groups:

- PBO
  - Disc (including subjects who were randomized to PBO and discontinued in Initial Period)
  - PBO (including subjects who were randomized to PBO, continued in Maintenance Period; the sample size (Nobs) for observed results may decrease because of escapers after Week 16 or withdrawals in Maintenance Period)
  - Esc (including subjects who were randomized to PBO and escaped at or after Week 16; the sample size (Nobs) observed results may increase in time because of escapers after Week 16 or decrease because of withdrawals)
  - All PBO (including all subjects randomized to PBO in Initial Period)
- CZP 200mg Q2W
  - Disc (including subjects who were randomized to CZP 200mg Q2W and discontinued in Initial Period)
  - CZP 200mg Q2W (including subjects who were randomized to CZP 200mg Q2W, re-randomized to CZP 200mg Q2W in Maintenance Period; the sample size (Nobs) for observed results may decrease because of escapers after Week 16 or withdrawals in Maintenance Period)
  - CZP 400mg Q4W (including subjects who were randomized to CZP 200mg Q2W, re-randomized to CZP 400mg Q4W in Maintenance Period; the sample size (Nobs) for observed results may decrease because of escapers after Week 16 or withdrawals in Maintenance Period)
  - Esc (including subjects who were randomized to CZP 200mg Q2W and escaped at or after Week 16; the sample size (Nobs) observed results may increase in time because of escapers after Week 16 or decrease because of withdrawals)
  - All CZP 200mg Q2W (including all subjects randomized to CZP 200mg Q2W in Initial Period)
- CZP 400mg Q2W
  - Disc (including subjects who were randomized to CZP 400mg Q2W and discontinued in Initial Period)
  - CZP 400mg Q2W (including subjects who were randomized to CZP 400mg Q2W, continued in Maintenance Period; the sample size (Nobs) for observed results may decrease because of escapers after Week 16 or withdrawals in Maintenance Period)
  - Esc (including subjects who were randomized to CZP 400mg Q2W and escaped at or after Week 16; the sample size (Nobs) observed results may increase in time because of escapers after Week 16 or decrease because of withdrawals)

– All CZP 400mg Q2W (including all subjects randomized to CZP 400mg Q2W in Initial Period)

Data will be summarized based on observed and NRI data.

8.3.2 PGA Clear or Almost Clear (with at least 2 category improvement) by Visit

See Section 8.2.1 for details of the derivation of PGA Clear or Almost Clear (with at least 2 category improvement).

Initial Period

PGA responder rates will be summarized by randomized treatment group for the FAS at each time point (Weeks 2, 4, 8, 12 and 16). A comparison between treatment groups will be made at each time point using the same model and approach for handling missing data as described for the primary analysis. The estimate for the responder rate, the odds ratio, 95% CI, and p-value from the model will be presented. Additionally, the responder rates based on the observed data will be summarized using counts and percentages. Each time point will be analyzed separately. If convergence is not obtained due to lack of responders in one or more treatment groups, methods described in Section 8.1.2 will be applied instead.If the model still fails, percentages for the responders will be displayed. For EPS only descriptive statistics will be provided.

Line plots will be generated to present PGA responder rates (as derived by the above procedure) by randomized treatment group through Week 16.

Maintenance Period (Interim Analysis, excluding subjects who escaped at Week 16)

The summaries will include the observed responder rate at each visit. Subjects who meet the criterion for escape (ie, not achieving PASI50 response) at Week 16 are excluded from the point of escape. For other missing data, multiple imputation will be performed based on MCMC methodology. The analysis (logistic regression) of response rate on MCMC imputed data is similar to the procedure outlined in Section 8.1.2 except that escape subjects are not considered here. The estimated responder rates and corresponding 95% confidence intervals for the difference in proportion of responder vs. PBO and odds ratios vs PBO with 95% confidence interval and p-value at each visit will be presented by blinded maintenance treatment group based on the FAS.

Additionally, NRI will be used for imputation of missing data. The estimated responder rates, odds ratios vs. PBO with corresponding 95% confidence interval and p-value at each visit in the Blinded Maintenance Period [ie, Week 16 through Week 24] will be presented by blinded maintenance treatment group at Week 16 based on the FAS.

PGA responder rates (based on simple counts and percentages only) will also be summarized for the Blinded Maintenance Period by blinded maintenance treatment group (combined group inclusive) using NRI imputed and observed case data.

A table summarizing (exact) logistic regression analysis results of PGA response rates during Blinded Maintenance Period based on the subset of PGA responders at Week 16 will also be provided (observed case, NRI and MCMC imputed data), procedure as outlined in Section 8.1.2. Additionally, the same table will be produced to summarize simple counts and percentages data using blinded maintenance treatment group (combined group inclusive) using NRI and observed case data only.

Line plots will be generated to present the percentages of responders over time by blinded maintenance treatment group over time (from Week 16 to Week 24) based on MCMC imputed data.

Maintenance Period (Final Analysis, including subjects who escaped after Week 16)

The analysis of the PGA responder rate during the Maintenance Period will be based on the FAS. Missing data will be handled based on a combination of NRI and multiple imputation using the same methods as described in the previous section for PASI.

The estimated responder rates at each week will be presented by treatment group based on the FAS.

Additionally, NRI will be used for imputation of missing data. Simple proportions will be used to estimate responder rates at each visit in the Maintenance Period (ie, Week 16 through Week 52). Responder rates based on observed case data will also be summarized.

A table summarizing the PGA response rates during Maintenance Period based on the subset of PGA responders at Week 16 will also be provided (observed case, NRI and MCMC imputed data).

Line plots will be generated to present the percentage of responders over time by maintenance treatment group over time (from Week 16 to Week 52) based on MCMC imputed data.

Combined Initial and Maintenance Period (Interim Analysis, excluding subjects who escaped at Week 16)

PGA responder rates will be summarized by randomized treatment group at each visit from Week 0 to Week 24 based on NRI and observed case data. Responder rates based on NRI data, odds ratios with corresponding 95% CIs will be derived without modelling but only by calculating counts, percentages and CIs. No p-values will be presented. For the NRI summary, subjects will be imputed as non-responders at the point of escape or for those subjects who do not escape, from the point of premature withdrawal through Week 24. For observed data, no imputation will be performed and counts and percentages of responders will be presented.

Escape Arm in Maintenance Period (Final Analysis, including data after escape for subjects who escaped at/after Week 16)

Observed PGA responder rates will be summarized by the treatment group before escape from Week 16 to Week 52 based on FAS. Observed results in maintenance period but before escape will not be included in this table.

Additionally, the observed PGA responder rates will be summarized by the treatment group before escape and by escape maintenance treatment group from Week 16 to Week 52 based on FAS. Due to up-titration, subjects may be presented in both escape maintenance treatment groups (Esc CZP 200mg Q2W, Esc CZP 400mg Q2W), so that the sum of the sample sizes of both treatment groups will exceed the number of escapers.

Combined Initial and Maintenance Period (Final Analysis, including subjects who escaped at/after Week 16)

PGA responder rates will be summarized by randomized treatment group at each visit from Week 0 to Week 52 based on NRI and observed case data. Responder rates based on NRI data will be derived without modelling but only by calculating counts and percentages. No p-values will be presented. For the NRI summary, subjects will be imputed as non-responders

at the point of escape or for those subjects who do not escape, from the point of premature withdrawal through Week 52. For observed data, no imputation will be performed and counts and percentages of responders will be presented.

Additionally, the same table will be produced at each visit from Week 0 to Week 52 based on FAS by the groups described in detail in the PASI Section 8.3.1. Data will be summarized based on observed and NRI data.

8.3.3 PASI score (absolute)

See Section 8.1 for details of the derivation.

Initial Period

The absolute PASI score and the (percentage) change from Baseline will be summarized by randomized treatment group at each time point through Week 16 for the FAS using descriptive statistics for continuous data. Missing data will be imputed using LOCF.

Observed case data (without LOCF) in the Initial Period will be presented using descriptive statistics for continuous data by visit and by randomized treatment group for FAS and EPS.

Line plots will be generated to present mean percent change from Baseline in PASI score by randomized treatment group through Week 16.

Maintenance Period

Results will be summarized by visit and blinded maintenance treatment group for the FAS using descriptive statistics for continuous data. LOCF will be used to impute all missing data.

Subjects who switch to the escape arm will have their data at the escape time point carried forward until the end of the treatment period.

Observed case data (without LOCF) in the Maintenance Period will be presented using descriptive statistics for continuous data by visit and by blinded maintenance treatment group or escape maintenance treatment group for the FAS and by maintenance treatment group for the EPS.

Line plots will be generated to present mean percent change from Baseline in PASI score by randomized treatment group (Initial Period treatment) over time (from Week 0 to Week 24/Week 52).

8.3.4 PGA score distribution

See Section 8.2.1 for details of the derivation. The summaries described in this section are based on observed data – no imputation will be performed.

Initial Period

The distribution of the PGA score (0, 1, 2, 3, or 4) will be summarized in shift tables comparing the change from Baseline versus post-Baseline (Weeks 2, 4, 8, 12 and 16) by randomized treatment group for the FAS and EPS. The shift tables will be provided for each time point.

Maintenance Period

The distribution of the PGA Score will be summarized in shift tables comparing the change from Baseline versus post-Baseline (Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52) by blinded maintenance or escape maintenance treatment group for the FAS and by maintenance treatment group for EPS. The shift tables will be provided for each time point.

8.3.5 Time to PASI50, Time to PASI75, Time to PASI90, Time to PASI100

See Section 8.1.1 for details of the derivation of PASI50, PASI75, PASI90 and PASI100 response.

Initial Period

Time to PASI50, PASI75, PASI90 and PASI100 response will be evaluated using Kaplan-Meier methods for the time in days to achieving the response, comparing each CZP dose to placebo. Time to PASI50, PASI75, PASI90 and PASI100 response will be defined as the time interval in days from Baseline until the first date when the given response is achieved. Subjects who discontinue prior to achieving a response will be censored at the date of study drug discontinuation. Subjects who reach the Week 16 visit without achieving a response will be censored at date of the Week 16 visit.

Between groups differences (ie, each CZP dose vs placebo) will be analyzed with the log-rank statistics. Median time to response will be presented for each randomized treatment group. Kaplan-Meier plots of the time to PASI50, PASI75, PASI90 and PASI100 response by treatment group will be provided.

8.3.6 BSA affected by PSO (absolute, percent change)

The BSA palm method will be used for the evaluation of BSA as follows:

Body surface area estimation uses the palm (subject's flat hand and thumb together, fingers included) as representing around 1% of the total BSA.

- Subject's palm = 1%
- Head and neck = 10% (10 palms)
- Upper extremities = 20 % (20 palms)
- Trunk = 30% (30 palms)
- Lower extremities = 40 % (40 palms)
- Total BSA = 100%

The investigator will evaluate the percentage involvement of psoriasis on each subject's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement) at Baseline, Week 16 and Week 52. BSA data will be summarized as observed – no imputation will be performed.

Initial Period

At Week 16 the absolute score, change from Baseline score (Week 16 – Baseline) and percentage change from Baseline score (change from Baseline at Week 16/Baseline) will be summarized by randomized treatment group based on the FAS and EPS using descriptive statistics for continuous data.

Maintenance Period

The absolute score, change from Baseline score (Post-Baseline – Baseline) and percentage change from Baseline score (change from Baseline/Baseline) will be summarized by visit (Week 16 and Week 52) and blinded or escape maintenance treatment group based on the FAS and also by maintenance treatment group based on EPS using descriptive statistics for continuous data.

8.3.7 Change from Baseline in DLQI, percent of subjects achieving MCID, and percent achieving DLQI remission

At each post Baseline visit, the change from Baseline in DLQI, percent of subjects achieving minimal clinically important difference (MCID), and percent of subjects achieving DLQI remission, will be reported. See Section 8.2.3 for the derivation of the change from Baseline in DLQI score.

Change from Baseline in DLQI

The approach for summarizing the actual scores and change from Baseline scores over time in DLQI for the Initial Period and the Maintenance Period on observed and LOCF imputed cases will follow the same approach used for summarizing PASI scores as described in Section 0. Percent change from Baseline will not be summarized, but results based on LOCF on CFAS will be provided. Note that the change from Baseline in DLQI at Week 16 is also a key secondary efficacy variable and will be subject to statistical testing as described in Section 4.5.

Treatment group comparisons for each CZP treatment group vs placebo will be performed using an analysis of covariance (ANCOVA) model with treatment group and prior biologic exposure as factors and Baseline DLQI score as a covariate. The least squares (LS) means and standard errors derived from the model will be presented for each treatment group. Additionally, adjusted mean treatment differences, corresponding confidence intervals, and p-values will be reported. Missing values will be imputed using LOCF.

A line plot will be generated to present adjusted mean change from Baseline in DLQI by randomized treatment group through Week 16.

Percent of subjects achieving MCID or DLQI remission

At a given visit, a subject will be considered to have achieved MCID if their individual improvement from Baseline score is ≥4. A 4-point improvement in the DLQI score (DLQI response) has been reported to be meaningful for the subject.

At a given visit, a subject will be considered to have achieved remission if their absolute DLQI score is <=1.

Initial Period

DLQI MCID responder rates and subjects with DLQI remission will be summarized by visit and randomized treatment group for the FAS and CFAS. Missing data will be imputed using NRI. A summary of corresponding results based on observed cases will be provided by visit and randomized treatment group for the FAS and CFAS.

A comparison between treatment groups vs Placebo will be made at each time point using logistic regression models based on NRI imputed data and observed data. The estimate for the responder rate, the odds ratio, 95% CI, and p-value from the model will be presented.

Maintenance Period

For the maintenance phase, MCID responder rates and subjects with DLQI remission will be summarized by visit and blinded maintenance treatment group for the FAS and CFAS. Missing data will be imputed using NRI. Additionally, a summary of corresponding results based on observed cases will be provided by visit and (blinded) maintenance treatment group for the FAS and CFAS, and by escape maintenance treatment group for the FAS.

8.3.8 Change from Baseline in Itch Numeric Rating Scale, percent of subjects achieving MCID or remission

At each post Baseline visit, the change from Baseline in Itch Numeric Rating Scale and percent of subjects achieving minimal clinically important difference (MCID) or remission, will be reported. See Section 8.2.4 for the derivation of the change from Baseline in Itch Numeric Rating Scale.

Change from Baseline in Itch Numeric Rating Scale

The approach for summarizing the actual and change from Baseline scores over time in Itch Numeric Rating Scale for the Initial Period and the Maintenance Period on observed and LOCF imputed cases will follow the same approach as used for summarizing PASI scores, described in Section 0. Percent change from Baseline will not be summarized, but results based on LOCF on CFAS will be provided. A line plot will be generated to present change from Baseline in itch severity by randomized treatment group through Week 16.

Percent of subjects achieving MCID, or remission

At a given visit, a subject will be considered to have achieved MCID if their individual improvement from Baseline score is ≥4. A 4-point improvement in the Itch Numeric Rating Scale has been reported to be meaningful for the subject.

At a given visit, a subject's remission is defined as reaching an Itch Numeric Rating Scale of zero.

The summary of the results for subjects achieving MCID or Itch Numeric Rating Scale remission will be done analogous to analysis described in Section 8.3.7.

8.3.9 ACR20, 50, 70 response criteria and change from Baseline in all individual ACR core components

For subjects with psoriatic arthritis (PsA), the American College of Rheumatology 20%/ 50%/70% response criteria (ACR20, ACR50, and ACR70) will be evaluated. The analysis will be based on the PsA Set and on the PsA Set including only subjects with 3 or more tender joints and 3 or more swollen joints at Baseline.

A subject will be considered an ACR20/50/70 responder if:

> The counts for both tender joint count (TJC) and swollen joint count (SJC) (68/66 joint counts) (Section 8.3.10) have reduced by 20/50/70% or more, respectively, from the Baseline assessment

and

> There is a 20%, 50%, 70% or greater improvement in at least 3 of the 5 remaining core set measures:
>
> – Physician's Global Assessments of Disease Activity (PhGADA, Section 8.3.11)
> – Patient's Global Assessments of Disease Activity (PGADA, Section 8.3.12),
> – Patient's Assessment of Arthritis Pain (PAP, Section 8.3.13),
> – Health Assessment Questionnaire Disability Index (HAQ-DI, Section 8.3.14),
> – C-reactive protein (CRP).

If any of these assessments have missing values, the ACR20/50/70 response will be determined on the basis of the non-missing values as stated above. If that is not possible, the

ACR response will be set to missing. Missing items for the components TJC, SJC, and HAQ-DI will be handled as described in Section 8.3.10 and Section 8.3.14.

The number of subjects with a ACR20/ACR50/ACR70 response will be tabulated by randomized treatment group and visit for the Initial Period and by blinded maintenance treatment group or escape maintenance treatment group for the Maintenance Period, based on observed data and NRI imputed data. The treatment differences: CZP 200mg Q2W – PBO and CZP 400mg Q2W - PBO and All CZP – PBO (and corresponding 95% CI and p-value) are estimated at every visit during Initial Period, using a standard two-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CI for the differences are constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

Line plots will be generated to present the percentages of responders over time by randomized treatment group for the Initial Period and by blinded maintenance treatment for the Maintenance Period based on NRI imputed data.

Tables for the absolute values and changes vs. Baseline will be provided for each of the core measures (swollen joint count, tender joint count, PhGADA, PGADA, PGAAP, HAQ-DI, CRP, mNAPSI and DAS28(CRP)) by treatment group and visit for the Initial and Maintenance Period based on Observed case and LOCF imputed data. The treatment differences vs. PBO (LSMeans, 95% CI, p-value) are estimated at every visit during Initial Period, using a ANCOVA model with treatment and prior biological exposure (yes, no) as factors and Baseline score as covariate.

Same tables will be provided for the Escape Arm.

8.3.10 Swollen and tender joint counts (66/68 joints evaluation)

The following 68 joints are to be examined for tenderness by the Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each arthritis assessment.

- Upper body (6): bilateral temporomandibular, sternoclavicular, and acromioclavicular joints
- Upper extremity (34): bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), metacarpophalangeals (MCP I, II, III, IV and V), thumb interphalangeals (IP), proximal interphalangeals (PIP II, III, IV and V) and distal interphalangeals (DIP, II, III, IV, and V)
- Lower extremity (28): bilateral hips, knees, ankles, tarsi (includes subtalar, transverse tarsal, and tarsometatarsal considered as a single unit), metatarsophalangeals (MTP I, II, III, IV, and V), great toe interphalangeals, and proximal and distalinterphalangeals (PIP II, III, IV, and V)

TJC is the sum of tender joints among the 68 joints. It ranges from 0 to 68.

The assessment for swelling is made on 66 joints from the above list. The hip joints are excluded. Artificial and ankylosed joints are excluded from both tenderness and swelling assessments.

SJC is the sum of swollen joints among the 66 joints. It ranges from 0 to 66.

Table 8–5: Swelling and tenderness grading

Grade	Swelling response (66)	Tenderness response (68)
0	None	None (not tender)
1	Detectable	Positive (tenderness)

If there are missing observations for tender or swollen joints then, for derivation of the tender or swollen joint count, the remaining observations will be assessed and weighted by dividing by the number of non-missing and by multiplying by 68 for the tender joint count and by 66 for the swollen joint count. If a joint is not evaluable at Baseline, then that joint is set to missing throughout the study.

For the analysis of this data, please refer to Section 8.3.9.

8.3.11 Physician's Global Assessment of Disease Activity (PhGADA, VAS)

The Investigator will assess the overall status of the subject with respect to their PsA signs and symptoms and functional capacity (considering both joint and skin components) using a VAS where 0 is "very good, asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."

For the analysis of this data, please refer to Section 8.3.9.

8.3.12 Patient's Global Assessment of Disease Activity (PGADA, VAS)

Subjects will score their Global Assessment of Disease Activity in response to the question, "Considering all the ways your arthritis affects you, please mark a vertical line on the scale below to show how you are feeling today", using a VAS where 0 is "very good, no symptoms" and 100 is "very poor, severe symptoms." The subject should be asked to consider both joint and skin components in their response to this question.

For the analysis of this data, please refer to Section 8.3.9.

8.3.13 Patient's Global Assessment of Arthritis Pain (PGAAP, VAS)

For subjects with psoriatic arthritis (PsA), the Patient's Assessment of Arthritis Pain VAS is part of the ACR core set of measures in arthritis (Felson et al, 1993).

The Pain VAS consists of a horizontal line 100mm in length on which subjects are asked to indicate the level of their arthritis pain at the day of the visit between 0 ("no pain") and 100 ("most severe pain"), in response to the question: "Please mark a vertical line on the scale below to show how much pain you have from your arthritis today" (Dworkin et al, 2008).

For the analysis of this data, please refer to Section 8.3.9.

8.3.14 Health Assessment Questionnaire Disability Index score

The Health Assessment Questionnaire-Disability Index (HAQ-DI) contains 20 items divided into 8 domains that measure: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Subjects are required to indicate the degree of difficulty they have experienced in each domain in the past week on a 4-point scale that ranges from 0 (without difficulty) to 3 (unable to do). Any individual score of less than 2 is adjusted to 2 if the activity requires assistance from another individual or the use of an assistive device. The

highest score in each category is then summed (0 to 24) and divided by the number of categories scored to give a score that ranges from 0 to 3 (Matsuda et al, 2003).

If the patient does not provide an answer for any questions within a category, no score will be provided for that category. The HAQ disability index will be calculated by dividing the sum of the category scores by the number of categories with at least 1 question answered. If fewer than 6 categories have responses, no disability score will be calculated. A lower HAQ disability score indicates an improvement in function.

Percent of subjects achieving HAQ-DI MCID

At a given visit a subject will be considered to have the minimum clinically important difference in HAQ-DI for PSA subjects if the difference is >=0.3 points (Meese, 2009). Tables will present Observed case and NRI imputed data.

For further details for the analysis of this data, please refer to Section 8.3.9.

Additionally, a line plot will be generated to present change from Baseline in HAQ-DI score by randomized treatment group through Week 24/52.

8.3.15 Disease Activity Score DAS28(CRP) (28 joints evaluation)

The DAS28(CRP) will be calculated using CRP (mg/L) (see Table 10–1) and the Patient's Global Assessment of Disease Activity (VAS) (see Section 8.3.12). The joint assessment utilized for the DAS calculation will be based on 28 of the joints assessed for the 66/68-joint assessments (see Protocol Section 9.7.3)

- Upper extremity (26): bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), MCP I, II, III, IV, and V, thumb interphalangeals (IP), PIP II, III, IV, and V
- Lower extremity (2): knees

using the same 2-point scale for the assessment of swelling and tenderness of each joint.

DAS28(CRP) is calculated as follows:

$$DAS28(CRP) = 0.56\text{x}\sqrt{TJC} + 0.28\text{x}\sqrt{SJC} + 0.014\text{xPGADA} + 0.36\text{xln}(\text{CRP} + 1) + 0.96$$

where TJC=tender joint count and SJC=swollen joint count.

The DAS28(CRP) will be evaluated for subjects with psoriatic arthritis (PsA). The analysis will be based on the PsA Set including only subjects with 3 or more tender joints and 3 or more swollen joints at Baseline on Observed case and LOCF imputed data.

- If there are missing observations for tender or swollen joints, then the remaining observations will be assessed and weighted by dividing by number of non-missing and by multiplying by 28.
- If a joint is not evaluable at Baseline, then that joint is set to missing throughout the study.
- If at least 1 item of DAS28(CRP) is available for a visit, LOCF will be applied to impute values of those individual components which are missing.
- For CRP values below the lower limit of quantification, half the lower limit will be used as the imputed value. The lower limit of quantification may vary depending on the assay used and the imputed value will vary with it. For example, if the value is

presented as <3.0, then 1.5 will be used and if <0.1 is presented, then 0.05 will be used.

The DAS28(CRP) Disease Activity Classification will be presented in the categories Remission: <2.6, LDA: ≥2.6 to ≤3.2, MDA: >3.2 to ≤5.1, HDA: >5.1 and Missing by visit and by randomized treatment group during Initial Period and by blinded maintenance or escape maintenance treatment group during Maintenance Period in Observed case data.

A line plot will be generated to present change from Baseline in DAS28(CRP) score by randomized treatment group through Week 24/52.

8.3.16 mNAPSI (change from Baseline)

Subjects with psoriatic nail disease will have a single target nail selected at the Baseline visit for evaluation using the modified Nail Psoriasis Severity Index (mNAPSI). The analysis of mNAPSI will be based on the Napsi Set (NAPSIS) on Observed case and LOCF imputed data. The nail selected at Baseline should be the most affected nail observed and should be the only one assessed during study. The target nail will be scored (0-3) for onycholysis/oil drop dyschromia, nail plate crumbling, and for pitting and will be scored (0 for "no" or 1 for "yes") for leukonychia, nail bed hyperkeratosis, splinter hemorrhages, and red spots in the lunula.

A mNAPSI score will be derived by summing up each of the 7 items (Score Range = 0 to 13). If 1 response item scored on the 0 to 3 scale is missing, the missing response will be substituted by the average of the 2 available responses. If 1 or 2 response items scored on the 0 to 1 scale are missing, the missing response(s) will be imputed by the average of the available responses. Otherwise, the mNAPSI will be set to missing.

Tables for the absolute values and changes vs. Baseline will be provided by visit and by randomized treatment group for the Initial Period and by blinded maintenance treatment group or escape maintenance treatment group for the Maintenance Period. The treatment differences vs. PBO (LSMeans, 95% CI, p-value) are estimated at every visit during Initial Period, using an ANCOVA model with treatment and prior biological exposure (yes, no) as factors and Baseline score as covariate.

8.3.17 Clinical Global Impression of Improvement (CGI-I)

The CGI-I is evaluated by the Investigators on a 4-point scale (remission, improved, no change, worsened) based on changes from the Baseline findings of PSO.

Frequency tables by visit and by randomized treatment group for the Initial Period as well as by visit and by maintenance treatment group for the Maintenance Period will be provided for the results of the Investigator's assessment based on the CFAS on Observed case data and NRI imputed data. Within NRI imputation, missing values are imputed with the category "No Change".

A line plot will be generated to present change from Baseline in CGI-I score by randomized treatment group through Week 24/52.

8.3.18 Global Improvement Score for Pustular PSO

The analysis will be based on the Generalized Pustular PSO Set (GPPS). The Global Improvement Score is evaluated by the Investigators as "very much improved," "much improved," "minimally improved," "no change," or "worsened" based on changes from the baseline JDA severity index scores and components, as presented in Table 8–6.

Table 8–6: Global Improvement Score

	Change in JDA Severity Classification Score		**Other criteria**
Very much improved	Reduction by ≥3 points	or	Clear or almost clear of signs of generalized pustular PSO
Much improved	Reduction of 1 or 2 points	or	At least 1 of the following: Erythema area with pustules (%) reduced by ≤30% compared to Baseline Clinically meaningful improvement in at least 2 other components of the JDA Severity Index for generalized pustular PSO (erythema area, edema area, WBC, CRP, albumin)
Minimally improved	0 points (no change)	and	At least 1 of the following: Erythema area with pustules (%) reduced by ≤20% compared to Baseline Clinically meaningful improvement in at least 1 other component of the JDA Severity Index for generalized pustular PSO (erythema area, edema area, WBC, CRP, albumin)
No change	0 points (no change)	and	Not meeting the other criteria of minimally improved
Worsened	≥+1 point	-	Not applicable

Frequency tables by visit and by randomized treatment group for the Initial Period as well as by visit and by maintenance treatment group for the Maintenance Period will be provided for the results of the Global Improvement Score based on the GPPS on Observed case data and NRI imputed data.

Within NRI imputation, missing values are imputed with the category "No Change".

8.3.19 JDA Severity Index Score for generalized pustular PSO

The JDA severity index score for generalized pustular PSO consists of area of erythema with pustules, area of erythema (total), area of edema, fever, WBC count, CRP, and serum albumin, as displayed in Table 8–7.

The total score of JDA severity index for generalized pustular PSO is assigned a score of 0 to17 (0=best, 17=worst).

Descriptive statistics for the absolute values and changes vs. Baseline will be provided by visit and by randomized treatment group for the Initial Period and by maintenance treatment group for the Maintenance Period based on GPPS on Observed case data and LOCF imputed data.

Table 8–7: JDA severity index or generalized pustular PSO

Severity classification	**Mild**	**Moderate**	**Severe**
A + B (combined scores)	0 to 6	7 to 10	11 to 17

Table 8–7: JDA severity index or generalized pustular PSO

A. Skin symptoms (total scores: 0 to 9)				
Scores	3	2	1	0
Erythematous area (BSA %)	≥75	≥25, <75	<25	0
Erythematous area with pustule (BSA %)	≥50	≥10, <50	<10	0
Edematous area (BSA %)	≥50	≥10, <50	<10	0
B. Systemic symptoms and laboratory findings (total scores: 0 to 8)				
Scores	2	1	0	
Fever (°C)	≥38.5	≥37.0, <38.5	<37.0	
WBC count (/μL)	≥15,000	≥10,000, <15,000	<10,000	
CRP (mg/dL)	≥7.0	≥0.3, <7.0	<0.3	
Serum albumin (g/dL)	<3.0	≥3.0,<3.8	≥3.8	

9 PHARMACOKINETICS AND IMMUNOLOGICAL PROCEDURES

9.1 Pharmacokinetics

9.1.1 Available data

Plasma samples for the measurement of the CZP concentration data will be taken at Baseline, Weeks 2, 4, 6, 8, 12, 16, 24, 32, 40, 52, EWD and SFU.

9.1.2 Analysis

CZP plasma concentration data will be tabulated and summarized by treatment group for each visit at which samples were taken using the geometric mean, geometric coefficient of variation, geometric mean, 95% confidence interval (CI), median, minimum, maximum. For each treatment group, geometric mean plasma concentration time curves will be plotted and spaghetti plots of plasma concentration time curves will be also plotted. Individual plasma concentration time curves will be plotted with ADA titers and PASI scores. The analysis will be based on the PK-PPS and CPKS.

Initial Period

Summaries based on PK-PPS will be presented for the following treatment groups:

- CZP 200mg Q2W
- CZP 400mg Q2W

The summaries for PK-PPS will be presented for all subjects and subjects with psoriatic arthritis.

Summaries based on CPKS will be presented for the following treatment groups:

- CZP 200mg Q2W

- CZP 400mg Q2W

The summaries for CPKS will be presented for subjects with generalized pustular or erythrodermic PSO.

Combined Initial and Maintenance Period

Summaries based on PK-PPS will be presented for the following treatment groups assigned at Week 0 or Week 16:

- CZP 200mg Q2W/CZP 200mg Q2W
- CZP 400mg Q2W/CZP 400mg Q2W
- CZP 200mg Q2W/CZP 400mg Q4W

Subjects who discontinued in Initial Period will be summarized in the treatment group assigned at Week 0 (e.g. discontinued CZP 200mg Q2W in CZP 200mg Q2W/CZP 200mg Q2W and discontinued CZP 400mg Q2W in CZP 400mg Q2W/CZP 400mg Q2W). Subjects who were randomized to CZP 200mg Q2W in Initial Period, but not re-randomized at Week 16, because of escape, are summarized in the treatment group CZP 200mg Q2W/CZP 200mg Q2W. Subjects who escape during the Maintenance Period will be summarized based upon the treatment group assigned at Week 0 or Week 16 (data at the escape visit and SFU data inclusive, regardless of increase in dose).

The summaries for PK-PPS will be presented for all subjects and subjects with psoriatic arthritis.

The summaries for PK-PPS will be presented by escape during the Maintenance Period for all subjects and subjects with psoriatic arthritis.

- Non-escapers from CZP 200mg Q2W/CZP 200mg Q2W
- CZP 200mg Q2W/Esc CZP
- Non-escapers from CZP 400mg Q2W/CZP 400mg Q2W
- CZP 400mg Q2W/Esc CZP
- Non-escapers from CZP 200mg Q2W/CZP 400mg Q4W
- CZP 400mg Q4W/Esc CZP

Summaries based on CPKS will be presented for the following treatment groups:

- Subjects who only receive CZP 200mg Q2W
- Subjects who only receive CZP 400mg Q2W

The summaries for CPKS will be presented for subjects with erythrodermic or generalized pustular PSO.

Analysis Considerations

Values below the lower limit of quantification (LLOQ) will be set to half the lower limit of quantification for the summaries. The geometric mean, geometric coefficient of variation, and geometric mean 95% CI will only be displayed if at least 2/3 of the data are above the LLOQ at a given time point. Data at the EWD visit will be summarized separately from the scheduled visits.

9.2 Immunological variable

9.2.1 Available data

Plasma samples for the measurement of anti-drug (CZP) antibodies (ADAs) will also be taken Baseline, Weeks 2, 4, 6, 8, 12, 16, 24, 32, 40, 52, EWD and SFU.

9.2.2 Anti-drug antibody classification

A cut point for a screening assay will be determined by the bioanalytical laboratory during assay validation. This cut point will be used to determine the screening status of anti-drug antibodies (ADAs) in the test sample as above the cut point (ACP) or below the cut point (BCP). For any test sample with a test result ACP, a further confirmatory assay will be performed, the results of which will be determined as either 'confirmed positive' (CP) or 'not confirmed positive' (NCP).

The following definitions will be applied regarding classification of test samples:

- An ADA status will be confirmed as positive for any sample with a test result ACP and CP
- An ADA status of negative will be concluded for any sample with a test result either BCP or ACP and NCP

Confirmed positive (CP) samples will be titrated. The dilution factor will be reported. The titer represents the last dilution factor of the sample's titration series still scoring positive in the screening ADA assay.

9.2.3 Subject classification

Subjects will receive an overall classification, inclusive of Baseline and Post-Baseline results, and be classified as follows based on the ADA assay results:

- ADA negative: no confirmed positive ADA samples at any of the sampling time points
- ADA positive: confirmed positive ADA samples at one or more sampling time points
- Missing: relevant samples are missing

Subject baseline classification will be based on the ADA assay test results at baseline

- Pre-ADA negative: negative ADA baseline sample
- Pre-ADA positive: confirmed positive ADA baseline sample
- Missing: no baseline ADA sample

Baseline is defined as the sample immediately prior to first treatment with CZP. For subjects randomized to CZP baseline will be Week 0 of the randomized treatment period and for subjects who were randomized to placebo but then received open-label CZP baseline will be Week 0 of escape.

Subjects will receive a treatment emergent classification based on the combination of the post-baseline ADA assay results as well as the baseline ADA sample result

- Treatment emergent ADA (TE-ADA) negative: (i) subjects with no confirmed positive ADA samples at any of the sampling time points, (ii) pre-ADA positive subjects with all post baseline samples either ADA negative or confirmed positive ADA but with a titer below a pre-defined fold increase from the Baseline value (the fold increase from

Baseline required to meet this criterion will be defined with the development of the assay and will be included in the TFLs)

- Treatment emergent ADA (TE-ADA) positive: (i) pre-ADA negative subjects with one or more confirmed positive samples post baseline, (ii) pre-ADA positive subjects with one or more confirmed positive ADA sample post baseline with a titer above a pre-defined fold increase from the Baseline value (the fold increase from Baseline required to meet this criterion will be the same as that defined for treatment emergent ADA negative and will be included in the TFLs)
- Missing: relevant samples are missing

9.2.4 Analysis

The number and percentage of subjects in the above classifications (pre-ADA and TE-ADA) will be reported. The first occurrence of TE-ADA positivity and the cumulative proportion of subjects having TE-ADA positivity will be presented by visit. For the first occurrence, each TE-ADA positive subject will be counted only once at the visit where TE-ADA positivity was first observed.

Initial Period

Summaries based on PK-PPS will be presented for the following treatment groups:

- CZP 200mg Q2W
- CZP 400mg Q2W
- All CZP

The summaries for PK-PPS will be presented for all subjects and subjects with psoriatic arthritis.

Summaries based on CPKS will be presented for the following treatment groups:

- CZP 200mg Q2W
- CZP 400mg Q2W
- All CZP

The summaries for CPKS will be presented for subjects with generalized pustular or erythrodermic PSO.

Combined Initial and Maintenance Period

Summaries based on PK-PPS will be presented for the following treatment groups assigned at Week 0 or Week 16:

- CZP 200mg Q2W/CZP 200mg Q2W
- CZP 200mg Q2W/CZP 400mg Q4W
- CZP 400mg Q2W/CZP 400mg Q2W
- All CZP

Subjects who discontinued in Initial Period will be summarized in the treatment group assigned at Week 0 (e.g. discontinued CZP 200mg Q2W in CZP 200mg Q2W/CZP 200mg Q2W and discontinued CZP 400mg Q2W in CZP 400mg Q2W/CZP 400mg Q2W). Subjects who were randomized to CZP 200mg Q2W in Initial Period, but not re-randomized at Week

16, because of escape, are summarized in the treatment group CZP 200mg Q2W/CZP 200mg Q2W. Subjects who escape during the Maintenance Period will be summarized based upon the treatment group assigned at Week 0 or Week 16 (data at the escape visit and SFU data inclusive, regardless of up titration).

The summaries for PK-PPS will be presented for all subjects and subjects with psoriatic arthritis.

Summaries based on CPKS will be presented for the following treatment groups:

- Subjects who only receive CZP 200mg Q2W
- Subjects who only receive CZP 400mg Q2W
- Subjects who switch from CZP 200mg Q2W to CZP 400mg Q2W
- All CZP

The summaries for CPKS will be presented for subjects with generalized pustular or erythrodermic PSO.

Analysis Considerations

Data at the EWD visit will be summarized separately from the scheduled visits.

9.3 Relationship between immunogenicity and pharmacokinetics

The results of the interim analysis demonstrated that almost all subjects showed TE-ADA positivity regardless of treatments and psoriatic subgroups and the relationship between immunogenicity and pharmacokinetics could not be investigated sufficiently using the summaries of CZP plasma concentrations by TE-ADA status. The subjects who had TE-ADA positivity showed various ADA titer values, therefore, the relationship between immunogenicity and pharmacokinetics will be investigated using the ADA titer values.

A scatter plot will be prepared between CZP concentrations (Y-axis) versus ADA titers (X-axis) until Week 16 without baseline and SFU for combined PK-PPS and CPKS. The X-axis will present the logarithm of the ADA titer to base 2. Symbols will present the treatment groups.

Maximum ADA titers until Week 16 or Week 52 will be derived by subject. For the derivation of maximum ADA titers, a missing ADA titer value will be imputed by 0.5 when the sample was negative.

A scatter plot will be prepared between dose-normalized CZP concentrations at Week 16 (concentration/dose, either 200 or 400; Y-axis) versus maximum ADA titers (X-axis) until Week 16 without baseline and SFU for combined PK-PPS and CPKS. The X-axis will present the logarithm of the maximum ADA titer to base 2.

A box plot will be prepared between dose-normalized CZP concentrations at Week 16 (concentration/dose; Y-axis) versus maximum ADA titers (X-axis) until Week 16 without baseline and SFU for combined PK-PPS and CPKS. The X-axis will present the logarithm of the maximum ADA titer to base 2.

Based on the maximum ADA titers, subjects will be categorized into the following subgroups:

- Low: maximum ADA titer <= 1024
- High: maximum ADA titer > 1024

For the Initial Period or the Combined Initial and Maintenance Period, the maximum ADA titers until Week 16 or Week 52, respectively, will be used for the categorization.

CZP plasma concentration data will be tabulated and summarized by treatment group and visit and by maximum ADA titer category within the treatment group using the geometric mean, geometric coefficient of variation, geometric mean 95% confidence interval (CI), median, minimum and maximum. For each treatment group, geometric mean plasma concentration time curves will be plotted by maximum ADA titer category.

Initial Period

Summaries based on PK-PPS will be presented for the following treatment groups:

- CZP 200mg Q2W
- CZP 400mg Q2W

The summaries for PK-PPS will be presented for all subjects and subjects with psoriatic arthritis.

Summaries based on CPKS will be presented for the following treatment groups:

- CZP 200mg Q2W
- CZP 400mg Q2W

The summaries for CPKS will be presented for subjects with generalized pustular or erythrodermic PSO.

Combined Initial and Maintenance Period

Summaries based on PK-PPS will be presented for the following treatment groups assigned at Week 0 or Week 16:

- CZP 200mg Q2W/CZP 200mg Q2W
- CZP 200mg Q2W/CZP 400mg Q4W
- CZP 400mg Q2W/CZP 400mg Q2W

Subjects who discontinued in Initial Period will be summarized in the treatment group assigned at Week 0 (e.g. discontinued CZP 200mg Q2W in CZP 200mg Q2W/CZP 200mg Q2W and discontinued CZP 400mg Q2W in CZP 400mg Q2W/CZP 400mg Q2W). Subjects who were randomized to CZP 200mg Q2W in Initial Period, but not re-randomized at Week 16, because of escape, are summarized in the treatment group CZP 200mg Q2W/CZP 200mg Q2W. Subjects who escape during the Maintenance Period will be summarized based upon the treatment group assigned at Week 0 or Week 16 (data at the escape visit and SFU data inclusive, regardless of up titration).

The summaries for PK-PPS will be presented for all subjects and subjects with psoriatic arthritis.

Summaries based on CPKS will be presented for the following treatment groups:

- Subjects who only receive CZP 200mg Q2W
- Subjects who only receive CZP 400mg Q2W

The summaries for CPKS will be presented for subjects with generalized pustular or erythrodermic PSO.

Analysis Considerations

Values below the lower limit of quantification (LLOQ) will be set to half the lower limit of quantification for the summaries. The geometric mean, geometric coefficient of variation, and geometric mean 95% CI will only be displayed if at least 2/3 of the data are above the LLOQ at a given time point. Data at the EWD visit will be summarized separately from the scheduled visits.

9.4 Relationship between immunogenicity and efficacy variables

The results of the interim analysis demonstrated that almost all subjects showed TE-ADA positivity regardless of treatments and psoriatic subgroups and the relationship between immunogenicity and efficacy variables could not be investigated sufficiently using the summaries of Anti-CZP Antibody Titer. The subjects who had TE-ADA positivity showed various ADA titer values, therefore, the relationship between immunogenicity and efficacy variables will be investigated using the ADA titer values.

The definition of Maximum ADA titers is the same as in Section 9.3.

Maximum ADA titers are classified based on measured values and aggregated in the following categories.

- Low: maximum ADA titer <= 1024
- High: maximum ADA titer > 1024

The constitution of the treatment group of Week 16 conforms to the treatment group of Initial Period and the constitution of the treatment group of Week 24/Week 52 conforms to the treatment group of Combined Initial and Maintenance Period of Section 9.2.4.

For the efficacy variable, frequency counting is performed on Maximum ADA titer and Maximum ADA titer category for each analysis set and treatment group.

- Subjects with plaque PSO
  - Population: plaque PSO
    Analysis Set: Pharmacokinetics Per-Protocol Set

    Efficacy variables: PASI75 (Non-Responder Rate), PASI90 (Non-Responder Rate), PGA (Non-Responder Rate)
  - Population: PsA Subjects with 3 or more tender joints and 3 or more swollen joints at Baseline)
    Analysis Set: Pharmacokinetics Per-Protocol Set (PsAS (Subjects with 3 or more tender joints and 3 or more swollen joints at Baseline))

    Efficacy variable: ACR20 (Non-Responder Rate)
- Subjects with erythrodermic PSO or generalized pustular PSO
  - Population: Erythrodermic PSO
    Analysis Set: Cohort Pharmacokinetics Set (Erythrodermic PSO Set)

    Efficacy variables: PASI75 (Non-Responder Rate), PASI90 (Non-Responder Rate), PGA (Non-Responder Rate)
  - Population: Generalized Pustular PSO
    Analysis Set: Cohort Pharmacokinetics Set (Generalized Pustular PSO Set)

    Efficacy variable: Global Improvement Score (Non-Responder Rate)

Analysis Considerations

Data at the EWD visit will be summarized separately from the scheduled visits.

9.5 Relationship between immunogenicity and safety

The results of the interim analysis demonstrated that almost all subjects showed TE-ADA positivity regardless of treatments and psoriatic subgroups and the relationship between immunogenicity and safety could not be investigated sufficiently using the summaries of Anti-CZP Antibody Titer.

For further details regarding this analysis, refer to Section 10.2.

10 SAFETY ANALYSES

10.1 Extent of exposure

Summaries for exposure will be presented as the number of days exposed to study medication, number of days dose received, and the patient exposure days at risk for the Initial Period, the Maintenance Period, and the Combined Initial and Maintenance Period. For the Maintenance Period, data will be summarized separately for exposure to blinded study medication and exposure to open-label study medication. For the Combined Initial and Maintenance Period, data will be summarized separately for exposure to just blinded treatment and exposure to both blinded and open-label treatment combined. Additionally, the total patient exposure years at risk will be provided for each of the periods.

Throughout this section, date of last clinical contact for each subject is defined as the maximum of (last visit date including SFU visits, last AE start date (considering imputed dates and non-imputed dates), date of study termination or completion, last date of study drug administration) taking scheduled and unscheduled visits into account.

10.1.1 Interim Analysis

Initial Period

Duration of exposure (days) to study medication, number of days dose received, and patient exposure days at risk during the Initial Period will be summarized by randomized treatment group for the SS, PsAS and CSS. Week 14 is the intended last administration of study medication for this period. The calculations will be as follows:

Duration of exposure:

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

The 14 days are included in the formula as this is the dosing interval in the Initial Period.

If the date of last administration of study medication + 14 days extends to a date beyond the Week 16 study medication administration date, then this calculation reverts to:

- Week 16 study medication administration date – date of first administration of study medication.

For subjects who die during the Initial Period, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to:

- Date of death – date of first administration of study medication +1.

Number of days a dose was received: The total number of dose days from Baseline (Week 0) up to Week 14 (inclusive).

Patient exposure days at risk:

For subjects who complete the Week 16 visit and continue to the Maintenance Period:

- Date of Week 16 administration of study medication – date of first administration of study medication.

For subjects who discontinue on or prior to the Week 16 visit, use the minimum of the following:

- Date of last administration of study medication – date of first administration of study medication + 70 days
- 112 days (equivalent to intended 16-week Initial Period)
- Date of last clinical contact – date of first administration of study medication + 1.

For subjects who die prior to the Week 16 visit:

- Date of death – date of first administration of study medication + 1.

Maintenance Period

Duration of exposure (days) to study medication and number of days dose was received during the Maintenance Period will be summarized by blinded maintenance treatment group for the SS, PsAS and the CSS. Week 22 is the intended last administration of study medication for this period in the interim analysis. The calculations will be as follows:

Duration of exposure:

- Date of last administration of study medication – date of Week 16 administration of study medication + 14 days

The 14 days are included in the formula as this is the dosing interval in the Maintenance Period.

If the date of last administration of study medication + 14 days extends to a date beyond the Week 24 visit, then this calculation reverts to:

- Date of Week 24 visit – date of Week 16 administration of study medication

For subjects who die during the Maintenance Period, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to:

- Date of death – date of Week 16 administration of study medication +1.

Number of days a dose was received: The total number of dose days from Week 16 up to Week 22 (inclusive).

Patient exposure days at risk:

For subjects who complete the Week 24 visit:

- Date of Week 24 visit – date of Week 16 administration of study medication.

For subjects who discontinue on or prior to the Week 24 visit, use the minimum of the following:

- Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
- 56 days (equivalent to intended 8-week Maintenance Period)

– Date of last clinical contact – date of Week 16 administration of study medication + 1.

For subjects who die prior to the Week 24 visit:

– Date of death – date of Week 16 administration of study medication + 1.

Combined Initial and Maintenance Period

Duration of exposure (days) to study medication and number of days dose was received during the Combined Initial and Maintenance Period will be summarized by combined treatment group as given in Section 3.6.1 for the SS, PsAS and CSS. The calculations will be as follows:

Week 24 is the intended last date of study medication administration for the interim analysis.

Duration of exposure to placebo:

For subjects who were randomized to placebo, did not escape at Week 16, and are ongoing at Week 24:

– Date of Week 22 administration of study medication – date of Week 0 administration of study medication + 14 days

For subjects who were randomized to placebo, did not escape at Week 16, and are not ongoing at Week 24:

– Date of last administration of study medication – date of Week 0 administration of study medication + 14 days

For subjects randomized to placebo who escaped to CZP 200mg Q2W at Week 16:

Date of Week 16 visit – date of Week 0 administration of study medication

Duration of exposure to CZP regardless of dose ("All CZP"):

For subjects who were randomized to placebo, escaped at Week 16, and are ongoing at Week 24:

– Date of last administration of study medication the Week 24 visit – date of Week 16 administration of study medication

For subjects who were randomized to placebo, escaped at Week 16, and are not ongoing at Week 24:

– Date of last administration of study medication – date of Week 16 administration of study medication + 14 days

For subjects who were randomized to CZP and are ongoing at Week 24:

– Date of Week 24 visit – date of Week 0 administration of study medication

For subjects who were randomized to CZP and are not ongoing at Week 24:

– Date of last administration of study medication – date of Week 0 administration of study medication + 14 days.

– For subjects who die, this calculation reverts to: date of death – date of first administration of CZP + 1 day.

Duration of exposure to CZP at a specific dose (CZP 200mg Q2W, CZP 400mg Q4W, CZP 400mg Q2W):

The exposure period for derivation of exposure at a specific dose corresponds to the period from the date of first injection of CZP at the specific dose level and through the date of last dose at that same specific dose level +14 days.

If a subject received the same dose of CZP in the Initial and Maintenance Periods of the study, then the first dose date will be taken from the Initial Period (Week 0) and the last dose date will be taken from the Maintenance Period.

- For subjects who are ongoing at Week 24, the last dose date is defined as the Week 24 administration date. Duration will be calculated as (date of Week 24 dose – date of first dose).
- For subjects who are not ongoing at Week 24, the last dose date is defined as the latest administration date. Duration will be calculated as (date of last dose – date of first dose + 14 days).

If a subject switches treatment (or dose) across the Initial and Maintenance Periods, then the total exposure to each given dose will be obtained by summing the exposure time at each specific dose in each individual study period.

- For subjects who complete the Week 16 visit and continue to the Maintenance Treatment Period: date of Week 16 administration of study medication – date of Week 0 administration of study medication is attributable to the original CZP treatment.
- For subjects who discontinue on or prior to the Week 16 visit: date of Week 14 administration (or latest administration date) – date of Week 0 administration + 14 days is attributable to the original CZP treatment.
- For subjects who complete the Week 24 visit: date of Week 24 administration of study medication – date of Week 16 administration of study medication is attributable to the CZP treatment assigned at Week 16.

For subjects who discontinue on or prior to the Week 24 visit: date of latest administration of study medication – date of Week 16 administration of study medication + 14 days is attributable to the CZP treatment assigned at Week 16.

Number of days a dose was received:

For subjects who were randomized to placebo, did not escape at Week 16, and are ongoing at Week 24:

- Total number of dose days from Week 0 up to Week 22 (inclusive) is attributable to placebo.

For subjects who were randomized to placebo, did not escape at Week 16, and are not ongoing at Week 24:

- Total number of dose dates from Week 0 up to last administration of placebo is attributable to placebo.

For subjects randomized to placebo who escaped to CZP 200mg Q2W at Week 16:

- Total number of dose days from Week 0 up to Week 14 (inclusive) is attributable to placebo
- Total number of dose days from Week 16 up to Week 22 (inclusive) is attributable to CZP 200mg Q2W. Note that if a subject withdrew prior to Week 24, then this

algorithm reverts to the total number of dose days from Week 16 up to last dose of CZP.

- For subjects randomized to CZP, this is defined as the total number of dose days from date of first administration of CZP to date of last administration of CZP (inclusive). This will be calculated for CZP (regardless of dose) as well as for each individual CZP dose.

Patient exposure days at risk to placebo:

- For subjects who were randomized to placebo, did not escape at Week 16, and are ongoing at Week 24:
  - Date of Week 24 visit – date of Week 0 administration of study medication
- For subjects who were randomized to placebo, did not escape at Week 16, and are not ongoing at Week 24, use the minimum of the following:
  - Date of last administration of study medication – date of Week 0 administration of study medication + 70 days.
  - 168 days (equivalent to the intended 24-week treatment period)
  - Date of last clinical contact – date of Week 0 administration of study medication + 1 day
- For subjects randomized to placebo who escaped to CZP 200mg Q2W at Week 16:
  - Date of Week 16 visit – date of Week 0 administration of study medication

Patient exposure days at risk to CZP regardless of dose ("All CZP"):

- For subjects who were randomized to placebo, escaped at Week 16, and are ongoing at Week 24:
  - Date of the Week 24 visit – date of Week 16 administration of study medication
- For subjects who were randomized to placebo, escaped at Week 16, and are not ongoing at Week 24, use the minimum of the following:
  - Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
  - 56 days (equivalent to the intended 8-week treatment period)
  - Date of last clinical contact – date of Week 16 administration of study medication + 1 day
- For subjects who were randomized to CZP and are ongoing at Week 24:
  - Date of Week 24 visit – date of Week 0 administration of study medication
- For subjects who were randomized to CZP and are not ongoing at Week 24, use the minimum of the following:
  - Date of last administration of study medication – date of Week 0 administration of study medication + 70 days.
  - 168 days (equivalent to the intended 24-week treatment period)
  - Date of last clinical contact – date of Week 0 administration of study medication + 1 day

- For subjects who die, this calculation reverts to:
  - Date of death – date of first administration of CZP + 1 day.

Patient exposure days at risk to CZP at a specific dose (CZP 200mg Q2W, CZP 400mg Q4W, CZP 400mg Q2W):

- For subjects randomized to placebo who escaped to CZP 200mg Q2W at Week 16:
  - For subjects who complete the Week 24 visit: date of Week 24 administration of study medication – date of Week 16 administration of study medication is attributable to CZP 200mg Q2W.
  - For subjects who discontinue prior to the Week 24 visit, the minimum of the following is attributable to CZP 200mg Q2W:
    - Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
    - 56 days (equivalent to the intended 8-week treatment period)
    - Date of last clinical contact – date of Week 16 administration of study medication + 1 day
  - For subjects who die prior to the Week 24 visit: date of death – date of Week 16 administration of study medication + 1 day
- For subjects randomized to CZP who do not switch CZP doses at Week 16:
  - For subjects who complete the Week 24 visit: date of Week 24 administration of study medication – date of Week 0 administration of study medication is attributable to the original CZP dose.
  - For subjects who discontinue prior to the Week 24 visit, the minimum of the following is attributable to the original CZP dose:
    - Date of last administration of study medication – date of Week 0 administration of study medication + 70 days
    - 168 days (equivalent to the intended 24-week treatment period)
    - Date of last clinical contact – date of Week 0 administration of study medication + 1 day
  - For subjects who die prior to the Week 24 visit: date of death – date of Week 0 administration of study medication + 1 day
- For subjects randomized to CZP 200mg Q2W who switch to CZP 400mg Q4W at Week 16:
  - Date of Week 16 administration – date of Week 0 administration is attributable to CZP 200mg Q2W.
  - For subjects who complete the Week 24 visit: date of Week 24 administration of study medication – date of Week 16 administration of study medication is attributable to CZP 400mg Q4W.
  - For subjects who discontinue prior to the Week 24 visit, the minimum of the following is attributable to CZP 400mg Q4W:

- Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
- 56 days (equivalent to the intended 8-week treatment period)
- Date of last clinical contact – date of Week 16 administration of study medication + 1 day

– For subjects who die prior to the Week 24 visit: date of death – date of Week 16 administration of study medication + 1 day is attributable to CZP 400mg Q4W

- For subjects randomized to CZP 400mg Q2W who escaped to CZP 200mg Q2W at Week 16:
  – Date of Week 16 administration – date of Week 0 administration is attributable to CZP 400mg Q2W.
  – For subjects who complete the Week 24 visit: date of Week 24 administration of study medication – date of Week 16 administration of study medication is attributable to CZP 200mg Q2W.
  – For subjects who discontinue prior to the Week 24 visit, the minimum of the following is attributable to CZP 200mg Q2W:
    - Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
    - 56 days (equivalent to the intended 8-week treatment period)
    - Date of last clinical contact – date of Week 16 administration of study medication + 1 day
  – For subjects who die prior to the Week 24 visit: date of death – date of Week 16 administration of study medication + 1 day is attributable to CZP 200mg Q2W

10.1.2 Final Analysis

General note which pertains to all exposure derivations: gaps in dosing will be ignored.

Initial period:

Plaque PSO subjects and cohort subjects

Duration of exposure:

For subjects who complete Initial Period:

– Date of Week 16 – date of first administration of study medication

For subjects who discontinued prior to Week 16:

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

For subjects who die during the Initial Period, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to:

– Date of death – date of first administration of study medication +1.

Number of days a dose was received:

- The total number of dose days from Baseline (Week 0) up to Week 14 (inclusive).

Patient exposure days at risk:

For subjects who complete the Week 16 visit and continue to the Maintenance Period:

- Date of Week 16 administration of study medication – date of first administration of study medication.

For subjects who discontinue on or prior to the Week 16 visit, use the minimum of the following:

- Date of last administration of study medication – date of first administration of study medication + 70 days
- Date of last clinical contact – date of first administration of study medication + 1.

For subjects who die prior to the Week 16 visit:

- Date of death – date of first administration of study medication + 1.

Maintenance Period

Plaque PSO and cohort subjects; considering open-label treatment only

Duration of exposure:

For subjects who only received open-label CZP 200mg Q2W:

- Date of last administration of open-label CZP 200mg Q2W treatment – date of first administration of open-label CZP 200mg Q2W treatment at/after Week 16 + 14 days is attributed to CZP 200mg Q2W.

  For subjects who die during the Maintenance Period, if date of last administration of open-label CZP 200mg Q2W + 14 days extends to a date beyond the date of death, then this calculation reverts to: date of death – date of first administration of open-label CZP 200mg Q2W at/after Week 16 + 1 day.

For subjects who only received open-label CZP 400mg Q2W:

- Date of last administration of open-label CZP 400mg Q2W treatment – date of first administration of open-label CZP 400mg Q2W treatment at/after Week 16 + 14 days is attributed to CZP 400mg Q2W.

  For subjects who die during the Maintenance Period, if date of last administration of open-label CZP 400mg Q2W + 14 days extends to a date beyond the date of death, then this calculation reverts to: date of death – date of first administration of open-label CZP 400mg Q2W at/after Week 16 + 1 day.

For subjects who received both open-label CZP 200mg Q2W and open-label CZP 400mg Q2W:

- Date of first administration of open-label CZP 400mg Q2W treatment – date of first administration of open-label CZP 200mg Q2W treatment at/after Week 16 is attributed to CZP 200mg Q2W.
- Date of last administration of open-label CZP 400mg Q2W treatment – date of first administration of open-label CZP 400mg Q2W treatment + 14 days is attributed to CZP 400mg Q2W.

  For subjects who die during the Maintenance Period, if date of last administration of open-label CZP 400mg Q2W + 14 days extends to a date beyond the date of death, then

this calculation reverts to: date of death – date of first administration of open-label CZP 400mg Q2W treatment + 1 day.

For subjects who ever received a dose of open-label CZP at either dose (200mg Q2W, 400mg Q2W):

- Date of last administration of open-label study medication – date of first administration of open-label study medication at/after Week 16 + 14 days is attributable to "All CZP".

For subjects who die during the Maintenance Period, if date of last administration of open-label study medication + 14 days extends to a date beyond the date of death, then this "All CZP" calculation reverts to: date of death – date of first administration of open-label treatment at/after Week 16 + 1 day.

Number of days a dose was received

For subjects who only received open-label CZP 200mg Q2W:

- The total number of dose days from Week 16 up to Week 50 (inclusive) considering just doses of open-label CZP 200mg Q2W received.

For subjects who only received open-label CZP 400mg Q2W:

- The total number of dose days from Week 16 up to Week 50 (inclusive) considering just doses of open-label CZP 400mg Q2W received.

For subjects who received both open-label CZP 200mg Q2W and open-label CZP 400mg Q2W:

- CZP 200mg Q2W: The total number of dose days from Week 16 up to Week 50 (inclusive) considering each open-label CZP 200mg Q2W dose received.
- CZP 400mg Q2W: The total number of dose days from Week 16 up to Week 50 (inclusive) considering each open-label CZP 400mg Q2W dose received.

For subjects who ever received a dose of open-label CZP at either dose (200mg Q2W, 400mg Q2W):

- All CZP: The total number of dose days from Week 16 up to Week 50 (inclusive) considering any open-label CZP dose received.

Patient exposure days at risk for open-label CZP regardless of dose ("All CZP"):

For subjects who complete the Week 52 visit:

- Date of Week 50 administration of study medication – date of first administration of open-label study medication at/after Week 16 + 70 days.
- If the subject did not receive a dose at Week 50, this algorithm reverts to: Date of last administration of study medication – date of first administration of open-label study medication at/after Week 16 + 70 days.

For subjects who discontinue on or prior to the Week 52 visit, use the minimum of the following:

- Date of last administration of study medication – date of first administration of open-label study medication at/after Week 16 + 70 days
- Date of last clinical contact – date of first administration of open-label study medication at/after Week 16 + 1 day.

For subjects who die prior to the Week 52 visit:

- Date of death – date of first administration of open-label study medication at/after Week 16 + 1 day.

Patient exposure time at risk for a specific CZP dose considering open-label dosing only:

For plaque PSO subjects who escape to CZP 200mg Q2W at/after Week 16 and never subsequently up-titrate to CZP 400mg Q2W, or for cohort subjects who remain on open-label CZP 200mg Q2W during Maintenance and never subsequently up-titrate to CZP 400mg Q2W, and who complete the Week 52 visit, the following will be attributed to open-label CZP 200mg Q2W:

- Date of Week 50 administration of open-label study medication – date of first administration of open-label study medication at/after Week 16 + 70 days
- If the subject did not receive a dose at Week 50, this algorithm reverts to: Date of last administration of study medication – date of first administration of open-label study medication at/after Week 16 + 70 days.

For plaque PSO subjects who escape to CZP 200mg Q2W at/after Week 16 and never subsequently up-titrate to CZP 400mg Q2W, or for cohort subjects who remain on open-label CZP 200mg Q2W during Maintenance and never subsequently up-titrate to CZP 400mg Q2W, and who discontinued prior to Week 52, use the minimum of the following which will be attributed to open-label CZP 200mg Q2W:

- Date of last administration of open-label study medication – date of first administration of open-label study medication at/after Week 16 + 70 days
- Date of last clinical contact – date of first administration of open-label study medication at/after Week 16 + 1 day

  For subjects who die prior to the Week 52 visit: Date of death – date of first administration of open-label study medication at/after Week 16 + 1 day.

For cohort subjects who remain on open-label CZP 400mg Q2W during Maintenance and who complete the Week 52 visit, the following will be attributed to open-label CZP 400mg Q2W:

- Date of Week 50 administration of open-label study medication – date of first administration of open-label study medication at/after Week 16 + 70 days
- If the subject did not receive a dose at Week 50, this algorithm reverts to: Date of last administration of study medication – date of first administration of open-label study medication at/after Week 16 + 70 days.

For cohort subjects who remain on open-label CZP 400mg Q2W during Maintenance and who discontinued prior to Week 52, use the minimum of the following which will be attributed to open-label CZP 400mg Q2W:

- Date of last administration of open-label study medication – date of first administration of open-label study medication at/after Week 16 + 70 days
- Date of last clinical contact – date of first administration of open-label study medication at/after Week 16 + 1 day

For subjects who die prior to the Week 52 visit: Date of death – date of first administration of open-label study medication at/after Week 16 + 1 day.

For plaque PSO subjects who escape to CZP 200mg Q2W at/after Week 16 and subsequently up-titrate to CZP 400mg Q2W, or for cohort subjects who subsequently up-titrate to CZP 400mg Q2W at/after Week 16, time at risk to each open-label dose will be calculated as follows:

- For open-label CZP 200mg Q2W: Date of first administration of open-label CZP 400mg Q2W treatment – date of first administration of open-label CZP 200mg Q2W study medication at/after Week 16.
- For CZP 400mg Q2W, if the subject completed the Week 52 visit:
    - Date of Week 50 administration of open-label CZP 400mg Q2W – date of first administration of open-label CZP 400mg Q2W at/after Week 16 + 70 days
    - If the subject did not receive a dose at Week 50, this algorithm reverts to: Date of last administration of open-label CZP 400mg Q2W – date of first administration of open-label CZP 400mg Q2W at/after Week 16 + 70 days.
- For CZP 400mg Q2W, if the subject discontinued prior to the Week 52 visit, use the minimum of the following:
    - Date of last administration of open-label CZP 400mg Q2W – date of first administration of open-label CZP 400mg Q2W at/after Week 16 + 70 days
    - Date of last clinical contact – date of first administration of open-label CZP 400mg Q2W at/after Week 16 + 1.

  For subjects who die prior to the Week 52 visit: Date of death – date of first administration of open-label CZP 400mg Q2W study medication at/after Week 16 + 1 day.

Maintenance Period

Plaque PSO subjects only; considering blinded treatment only

Duration of exposure

For subjects who started Maintenance, and did not escape at/after Week 16:

- Date of last administration of study medication – date of Week 16 administration of study medication + 14 days
- For subjects who die during the Maintenance Period, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of Week 16 administration of study medication + 1 day.

For subjects who started Maintenance, and did escape at/after Week 16:

- Date of first administration of open-label study medication – date of Week 16 administration of study medication.

Number of days a dose was received

For subjects who started Maintenance, and did not escape at/after Week 16:

- The total number of dose days from Week 16 up to Week 50 (inclusive).

For subjects who started Maintenance, and did escape at/after Week 16:

- The total number of dose days from Week 16 up to Week 50 (inclusive) considering just doses of blinded study medication received.

Patient exposure days at risk attributable to blinded treatment only

For subjects who started Maintenance, did not escape at/after Week 16, and complete the Week 52 visit:

- Date of Week 50 administration of study medication – date of Week 16 administration of study medication + 70 days.
- If the subject is missing their Week 50 injection date, then this algorithm reverts to: Date of last administration of study medication – date of Week 16 administration of study medication + 70 days.

For subjects who started Maintenance, did not escape at/after Week 16, and discontinue on or prior to the Week 52 visit, use the minimum of the following:

- Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
- Date of last clinical contact – date of Week 16 administration of study medication + 1.

For subjects who started Maintenance, did not escape at/after Week 16, and die prior to the Week 52 visit:

- Date of death – date of Week 16 administration of study medication + 1.

For subjects who started Maintenance, and did escape after Week 16:

- Date of first administration of open-label study medication – date of Week 16 administration of study medication.

Combined Initial and Maintenance Period

Plaque PSO subjects only; considering blinded treatment only

Duration of exposure

For subjects who discontinue on/prior to the Week 16 visit:

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

  For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who escape to open-label treatment at Week 16:

- Date of first administration of open-label study medication – date of first administration of blinded study medication

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance:

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

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not switch treatment (or dose) at Week 16 and who do escape during Maintenance:

- Date of first administration of open-label study medication – date of first administration of blinded study medication

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment.
- Date of last administration of study medication – date of Week 16 administration of study medication + 14 days is attributable to the treatment assigned at Week 16.

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of Week 16 administration of study medication + 1 day

For all subjects who do not escape during Maintenance:

- Date of last administration of study medication – date of first administration of study medication + 14 days is attributable to "All CZP".

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape during Maintenance:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment.
- Date of first administration of open-label study medication – date of Week 16 administration of study medication is attributable to the treatment assigned at Week 16.
- Date of first administration of open-label study medication – date of first administration of blinded study medication is attributable to "All CZP".

Number of days a dose was received

For subjects who discontinue on/prior to the Week 16 visit:

- Total number of dose days from Week 0 to last dose received (inclusive).

For subjects who escape at Week 16:

- Total number of dose days from Week 0 to last dose of blinded study medication received (inclusive).

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance:

- Total number of dose days from Week 0 to last dose received (inclusive).

For subjects who do not switch treatment (or dose) at Week 16 and who do escape during Maintenance:

- Total number of dose days from Week 0 to last dose of blinded study medication received (inclusive)

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance:

- Total number of dose days from Week 0 to Week 14 (inclusive) is attributable to the original treatment.
- Total number of dose days from Week 16 up to Week 50 (inclusive) is attributable to the treatment assigned at Week 16.

For all subjects who do not escape during Maintenance:

- Total number of dose days on CZP from Week 0 up to Week 50 (inclusive) is attributable to "All CZP".

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape during Maintenance:

- Total number of dose days from Week 0 to Week 14 (inclusive) is attributable to the original treatment.
- Total number of dose days from Week 16 through last dose of blinded study medication (inclusive) is attributable to the treatment assigned at Week 16.
- Total number of dose days from Week 0 through last dose of blinded study medication (inclusive) is attributable to "All CZP".

Patient exposure days at risk

For subjects who discontinue on/prior to the Week 16 visit, use the minimum of the following:

- Date of last administration of study medication – date of first administration of study medication + 70 days
- Date of last clinical contact – date of first administration of study medication + 1 day

  For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance, and who complete the Week 52 visit:

- Date of Week 50 administration of study medication – date of first administration of study medication + 70 days
- If the subject is missing their Week 50 injection date, then this calculation reverts to: Date of last administration of study medication – date of first administration of study medication + 70 days

  For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance, and who discontinue prior to the Week 52 visit, use the minimum of the following:

- Date of last administration of study medication – date of first administration of study medication + 70 days
- Date of last clinical contact – date of first administration of study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day.

For subjects who do not switch treatment (or dose) at Week 16 and who do escape during Maintenance:

- Date of first administration of open-label study medication – date of first administration of blinded study medication

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance, and who complete the Week 52 visit:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment.
- Date of Week 50 administration of study medication – date of Week 16 administration of study medication + 70 days is attributable to the treatment assigned at Week 16.
  - If the subject is missing their Week 50 injection date, then this calculation reverts to: Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
- Date of Week 50 administration of study medication – date of Week 0 administration of study medication + 70 days is attributable to "All CZP".
  - If the subject is missing their Week 50 injection date, then this calculation reverts to: Date of last administration of study medication – date of Week 0 administration of study medication + 70 days

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance, and who discontinue prior to completing the Week 52 visit:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment.
- For the treatment assigned at Week 16, use the minimum of the following:
  - Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
  - Date of last clinical contact – date of Week 16 administration of study medication + 1 day
- For "All CZP", use the minimum of the following:
  - Date of last administration of study medication – date of Week 0 administration of study medication + 70 days
  - Date of last clinical contact – date of Week 0 administration of study medication + 1 day

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape during Maintenance:

- Date of Week 16 administration of study medication – date of Week 0 administration of study medication is attributable to the original treatment.
- Date of first administration of open-label study medication – date of Week 16 administration of study medication is attributable to the treatment assigned at Week 16.
- Date of first administration of open-label study medication – date of first administration of study medication is attributable to "All CZP".

Combined Initial and Maintenance Period

Plaque PSO subjects; considering blinded + open-label treatment

Note that the algorithms described in this section may occasionally reference "blinded" doses of CZP and "open-label" doses of CZP in order to clearly outline the derivations. However, for the purposes of these calculations (duration of exposure, number of doses received, exposure time at risk), there is to be no distinction between exposures to blinded treatment and exposures to open-label treatment. Exposure to each treatment received is to be calculated regardless of whether it was administered as blinded or open-label treatment.

Duration of exposure

For subjects who discontinue on/prior to the Week 16 visit:

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

  For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance:

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

  For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of study medication + 1 day.

For subjects who do not switch treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do not subsequently up-titrate to CZP 400mg Q2W:

- Date of first administration of open-label study medication – date of first administration of blinded study medication is attributable to the original treatment.
- Date of last administration of open-label study medication – date of first administration of open-label study medication + 14 days is attributable to CZP 200mg Q2W.
- If the subject was initially randomized to CZP 200mg Q2W then this algorithm reverts to: date of last administration of study medication – date of first administration of study medication +14 days, all of which is attributable to CZP 200mg Q2W.

– Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of CZP study medication + 1 day.

For subjects who do not switch treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do subsequently up-titrate to CZP 400mg Q2W:

– Subjects who were initially randomized to CZP 200mg Q2W at Week 0:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of study medication is attributable to the original treatment (CZP 200mg Q2W).
  - Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 14 days is attributable to CZP 400mg Q2W.
  - Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

  For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

– Subjects who were initially randomized to CZP 400mg Q2W at Week 0:
  - [Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded CZP 400mg Q2W study medication] + [Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 14 days] is attributable to the original treatment (CZP 400mg Q2W).
    (1) For subjects who die, if date of last administration of open-label CZP 400mg Q2W study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

– Subjects who were not initially randomized to CZP 200mg Q2W or CZP 400mg Q2W at Week 0:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded study medication is attributable to the original treatment.
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.

- Date of last administration of study medication – date of first administration of open-label CZP 400mg Q2W study medication + 14 days is attributable to CZP 400mg Q2W.
  - (1) For subjects who die, if date of last administration of open-label CZP 400mg Q2W study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.
- Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment.
- Date of last administration of study medication – date of Week 16 administration of study medication + 14 days is attributable to the treatment assigned at Week 16.
- Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of Week 16 administration of study medication + 1.

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do not subsequently up-titrate to CZP 400mg Q2W:

- [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of last administration of open-label study medication – date of first administration of open-label study medication + 14 days)] is attributable to CZP 200mg Q2W.
  - For subjects who die, if date of last administration of open-label study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of open-label study medication + 1.
- Date of first administration of open-label CZP 200mg Q2W study medication – date of Week 16 administration of blinded study medication is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
- Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do subsequently up-titrate to CZP 400mg Q2W:

- [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication)] is attributable to CZP 200mg Q2W.

- Date of first administration of open-label CZP 200mg Q2W study medication – date of Week 16 administration of blinded study medication is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
- Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 14 days is attributable to CZP 400mg Q2W.
  - For subjects who die, if date of last administration of open-label CZP 400mg Q2W study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1.
- Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

For subjects who escape at Week 16 and who do not subsequently up-titrate during Maintenance:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment.
- Date of last administration of study medication – date of Week 16 administration of study medication + 14 days is attributable to the treatment assigned at Week 16.
- If the subject was initially randomized to CZP 200mg Q2W then this algorithm reverts to: date of last administration of study medication – date of first administration of study medication +14 days, all of which is attributable to CZP 200mg Q2W.
- Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of Week 16 administration of study medication + 1.

For subjects who escape at Week 16 and who do subsequently up-titrate during Maintenance:

- If the subject was initially randomized to CZP 200mg Q2W:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of blinded CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 14 days is attributable to CZP 400mg Q2W.
    (1) For subjects who die, if date of last administration of open-label CZP 400mg Q2W study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1.
  - Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".
- If the subject was initially randomized to CZP 400mg Q2W:

- Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W
- [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 14 days)] is attributable to CZP 400mg Q2W
- Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

– If the subject was not initially randomized to either CZP 200mg Q2W or CZP 400mg Q2W:
  - Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment.
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of Week 16 administration of study medication is attributable to CZP 200mg Q2W.
  - Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 14 days is attributable to CZP 400mg Q2W.

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of last administration of open-label CZP 400mg Q2W study medication + 1 day.

– For all subjects regardless of what dose they were initially randomized to:
  - Date of last administration of study medication – date of first administration of CZP study medication + 14 days is attributable to "All CZP".

Number of days a dose was received

For subjects who discontinue on/prior to the Week 16 visit:

– Total number of dose days from Week 0 to last dose received (inclusive).

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance:

– Total number of dose days from Week 0 to last dose received (inclusive).

For subjects who do not switch treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance but do not subsequently up-titrate to CZP 400mg Q2W:

– Total number of dose days from Week 0 to last dose of blinded study medication received (inclusive) is attributable to the original treatment
– Total number of dose days from escape through last dose received is attributable to CZP 200mg Q2W
– Note that if the subject was initially randomized to CZP 200mg Q2W then this algorithm reverts to: total number of dose days from Week 0 to last dose received (inclusive), all of which is attributable to CZP 200mg Q2W.

For subjects who do not switch treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do subsequently up-titrate to CZP 400mg Q2W:

- Total number of dose days from Week 0 to last dose of blinded study medication received (inclusive) is attributable to the original treatment
- Total number of dose days for open-label CZP 200mg Q2W is attributable to CZP 200mg Q2W
- Total number of dose days for open-label CZP 400mg Q2W is attributable to CZP 400mg Q2W
- Note that if the subject was initially randomized to CZP 200mg Q2W then the total number of dose days for CZP 200mg Q2W reverts to: total number of dose days from Week 0 to last open-label dose of CZP 200mg Q2W received (inclusive).
- Note that if the subject was initially randomized to CZP 400mg Q2W then the total number of dose days for CZP 400mg Q2W reverts to: total number of dose days from Week 0 to first open-label dose of CZP 200mg Q2W received (inclusive) + total number of dose days for open-label CZP 400mg Q2W.

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance:

- Total number of dose days from Week 0 to Week 14 (inclusive) is attributable to the original treatment (CZP 200mg Q2W).
- Total number of dose days from Week 16 up to Week 50 (inclusive) is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
- Total number of dose days from Week 0 up to Week 50 (inclusive) is attributable to "All CZP".

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance but do not subsequently up-titrate to CZP 400mg Q2W:

- Total number of dose days from Week 0 to Week 14 (inclusive) + while on open-label CZP 200mg Q2W is attributable to the original treatment.
- Total number of dose days from Week 16 through last dose of blinded study medication (inclusive) is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
- Total number of dose days from Week 0 through last dose received (inclusive) is attributable to "All CZP".

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do subsequently up-titrate to CZP 400mg Q2W:

- Total number of dose days from Week 0 to Week 14 (inclusive) + while on open-label CZP 200mg Q2W is attributable to the original treatment.
- Total number of dose days from Week 16 through last dose of blinded study medication (inclusive) is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).

- Total number of dose days while on open-label CZP 400mg Q2W study medication (inclusive) is attributable to CZP 400mg Q2W.
- Total number of dose days from Week 0 through last dose received (inclusive) is attributable to "All CZP".

For subjects who escape at Week 16 and do not subsequently up-titrate to CZP 400mg Q2W:

- Total number of dose days from Week 0 to Week 14 (inclusive) is attributable to the original treatment.
- Total number of dose days while on open-label CZP 200mg Q2W study medication (inclusive) is attributable to CZP 200mg Q2W.
- If the subject was initially randomized to CZP 200mg Q2W then this algorithm reverts to: Total number of dose days from Week 0 to Week 50 (inclusive), all of which is attributable to CZP 200mg Q2W.
- Total number of dose days from Week 0 through last dose received (inclusive) is attributable to "All CZP".

For subjects who escape at Week 16 and who do subsequently up-titrate to CZP 400mg Q2W:

- Total number of dose days from Week 0 to Week 14 (inclusive) is attributable to the original treatment.
- Total number of dose days while on open-label CZP 200mg Q2W study medication (inclusive) is attributable to CZP 200mg Q2W.
- Total number of dose days while on open-label CZP 400mg Q2W study medication (inclusive) is attributable to CZP 400mg Q2W.
- If the subject was initially randomized to CZP 200mg Q2W then this algorithm reverts to the sum of the total number of dose days while on CZP 200mg Q2W (either blinded or open-label).
- If the subject was initially randomized to CZP 400mg Q2W then this algorithm reverts to the sum of the total number of dose days while on CZP 400mg Q2W (either blinded or open-label).
- Total number of dose days from Week 0 through last dose received (inclusive) is attributable to "All CZP".

Patient exposure days at risk

For subjects who discontinue on/prior to the Week 16 visit, use the minimum of the following:

- Date of last administration of study medication – date of first administration of study medication + 70 days
- Date of last clinical contact – date of first administration of study medication + 1 day

  For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance, and who complete the Week 52 visit:

- Date of Week 50 administration of study medication – date of first administration of study medication + 70 days
- If the subject is missing their Week 50 injection date, then this calculation reverts to: Date of last administration of study medication – date of first administration of study medication + 70 days.

For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day.

For subjects who do not switch treatment (or dose) at Week 16 and who do not escape during Maintenance, and who discontinue prior to the Week 52 visit, use the minimum of the following:

- Date of last administration of study medication – date of first administration of study medication + 70 days
- Date of last clinical contact – date of first administration of study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not switch treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do not subsequently up-titrate to CZP 400mg Q2W:

- Subjects who were initially randomized to CZP 200mg Q2W at Week 0 who complete the Week 52 visit:
  - Date of Week 50 administration of study medication – date of first administration of study medication + 70 days
  - If the subject is missing their Week 50 injection then this algorithm reverts to: Date of last administration of study medication – date of first administration of study medication + 70 days

  For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day.
- Subjects who were initially randomized to CZP 200mg Q2W at Week 0 who discontinue prior to the Week 52 visit, use the minimum of the following:
  - Date of last administration of study medication – date of first administration of study medication + 70 days
  - Date of last clinical contact – date of first administration of study medication + 1 day

  For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day.
- Subjects who were not initially randomized to CZP 200mg Q2W at Week 0 who complete the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded study medication is attributable to the original treatment.

- Date of last administration of open-label CZP 200mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication + 70 days is attributable to CZP 200mg Q2W.

For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 200mg Q2W study medication + 1 day.

- Subjects who were not initially randomized to CZP 200mg Q2W at Week 0 who discontinue prior to the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded study medication is attributable to the original treatment.
  - For CZP 200mg Q2W time at risk, use the minimum of the following:
    (1) Date of last administration of open-label CZP 200mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first administration of open-label CZP 200mg Q2W study medication + 1 day

  For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 200mg Q2W study medication + 1 day.

For subjects who do not switch treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do subsequently up-titrate to CZP 400mg Q2W:

- Subjects who were initially randomized to CZP 200mg Q2W at Week 0 who complete the Week 52 visit:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of blinded CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - Date of Week 50 administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days is attributable to CZP 400mg Q2W.
  - If the Week 50 injection date is missing, then this calculation reverts to: Date of last administration of open-label CZP 400mg Q2W treatment – date of first administration of open-label CZP 400mg Q2W treatment + 70 days.

  For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.
- Subjects who were initially randomized to CZP 200mg Q2W at Week 0 who discontinue prior to the Week 52 visit, use the minimum of the following:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of blinded CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - For CZP 400mg Q2W time at risk, use the minimum of the following:
    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days

(2) Date of last clinical contact – date of first administration of open-label CZP 400mg Q2W study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

- Subjects who were initially randomized to CZP 400mg Q2W at Week 0 who complete the Week 52 visit:
  - [(Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded CZP 400mg Q2W study medication) + (Date of Week 50 (or last administration, if Week 50 is missing) administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days)] is attributable to CZP 400mg Q2W.
    (1) For subjects who die, this calculation reverts to: [(Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded CZP 400mg Q2W study medication) + (Date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day)].
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
- Subjects who were initially randomized to CZP 400mg Q2W at Week 0 who discontinue prior to the Week 52 visit, use the minimum of the following:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - For CZP 400mg Q2W time at risk, use (Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded CZP 400mg Q2W study medication) + the minimum of the following:
    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first administration of open-label CZP 400mg Q2W study medication + 1 day

    For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.
- Subjects who were not initially randomized to CZP 200mg Q2W or CZP 400mg Q2W at Week 0 who complete the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded study medication is attributable to the original treatment.
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.

- Date of Week 50 administration (or last administration, if Week 50 is missing) of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days is attributable to CZP 400mg Q2W.

For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

- Subjects who were not initially randomized to CZP 200mg Q2W or CZP 400mg Q2W at Week 0 who discontinue prior to the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of first administration of blinded study medication is attributable to the original treatment.
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - For CZP 400mg Q2W time at risk, use the minimum of the following:
    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first administration of open-label CZP 400mg Q2W study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance, and who complete the Week 52 visit:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment (CZP 200mg Q2W).
- Date of Week 50 administration (or last administration, if Week 50 is missing) of study medication – date of Week 16 administration of study medication + 70 days is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
  - For subjects who die, this calculation reverts to date of death – date of Week 16 administration of study medication + 1 day.
- Date of Week 50 administration (or last administration, if Week 50 is missing) of study medication – date of Week 0 administration of study medication is attributable to "All CZP".
  - For subjects who die, this calculation reverts to date of death – date of Week 0 administration of study medication + 1 day.

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do not escape during Maintenance, and who discontinue prior to completing the Week 52 visit:

- Date of Week 16 administration of study medication – date of first administration of study medication is attributable to the original treatment (CZP 200mg Q2W).
- For the treatment assigned at Week 16 (CZP 400mg Q4W), use the minimum of the following:

- Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
- Date of last clinical contact – date of Week 16 administration of study medication + 1 day
- For subjects who die, this calculation reverts to date of death – date of Week 16 administration of study medication + 1 day.

– For "All CZP", use the minimum of the following:
  - Date of last administration of study medication – date of Week 0 administration of study medication + 70 days
  - Date of last clinical contact – date of Week 0 administration of study medication + 1 day
  - For subjects who die, this calculation reverts to date of death – date of Week 0 administration of study medication + 1 day.

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do not subsequently up-titrate to CZP 400mg Q2W:

– Subjects who complete the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of Week 16 administration of blinded study medication is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
  - [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of Week 50 administration [or last administration, if Week 50 is missing] of open-label CZP 200mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication + 70 days)] is attributable to CZP 200mg Q2W.
  - For subjects who die, this calculation reverts to: [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of death – date of first administration of open-label CZP 200mg Q2W study medication + 1 day)] is attributable to CZP 200mg Q2W.

– Subjects who discontinue prior to the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of Week 16 administration of blinded study medication is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
  - For CZP 200mg Q2W time at risk, use (Date of Week 16 administration of study medication – date of first administration of study medication) + the minimum of the following:
    (1) Date of last administration of open-label CZP 200mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first administration of open-label CZP 200mg Q2W study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 200mg Q2W study medication + 1 day.

For subjects who do switch to a different blinded treatment (or dose) at Week 16 and who do escape to CZP 200mg Q2W during Maintenance and who do subsequently up-titrate to CZP 400mg Q2W:

- Subjects who complete the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of Week 16 administration of blinded study medication is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
  - Date of Week 50 administration (or last administration, if Week 50 is missing) of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days is attributable to CZP 400mg Q2W.
    (1) For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.
  - [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication)] is attributable to CZP 200mg Q2W.
- Subjects who discontinue prior to the Week 52 visit:
  - Date of first administration of open-label CZP 200mg Q2W study medication – date of Week 16 administration of blinded study medication is attributable to the treatment assigned at Week 16 (CZP 400mg Q4W).
  - [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication)] is attributable to CZP 200mg Q2W.
  - For CZP 400mg Q2W time at risk, use the minimum of the following:
    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first administration of open-label CZP 400mg Q2W study medication + 1 day

    For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

For subjects who escape at Week 16 and who do not subsequently up-titrate during Maintenance:

- If the subject was initially randomized to CZP 200mg Q2W and completes the Week 52 visit:
  - Date of Week 50 administration (or if Week 50 injection is missing, date of last administration) of study medication – date of first administration of study medication + 70 days.

For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day.

- If the subject was initially randomized to CZP 200mg Q2W and discontinued prior to the Week 52 visit, use the minimum of the following:
  - Date of last administration of study medication – date of Week 0 administration of study medication + 70 days
  - Date of last clinical contact – date of Week 0 administration of study medication + 1 day

  For subjects who die, this calculation reverts to date of death – date of first administration of CZP 200mg Q2W study medication + 1 day.
- If the subject was not initially randomized to CZP 200mg Q2W and completes the Week 52 visit:
  - Date of Week 16 administration of study medication – date of Week 0 administration of study medication is attributed to the original treatment
  - Date of Week 50 administration (or if Week 50 injection is missing, date of last administration) of study medication – date of Week 16 administration of study medication +70 days is attributed to CZP 200mg Q2W

  For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 200mg Q2W study medication + 1 day.
- If the subject was not initially randomized to CZP 200mg Q2W and discontinues prior to the Week 52 visit:
  - Date of Week 16 administration of study medication – date of Week 0 administration of study medication is attributed to the original treatment
  - For CZP 200mg Q2W, use the minimum of the following:
    (1) Date of last administration of study medication – date of Week 16 administration of study medication + 70 days
    (2) Date of last clinical contact – date of Week 16 administration of study medication + 1 day

    For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 200mg Q2W study medication + 1 day.

For subjects who escape at Week 16 and who do subsequently up-titrate during Maintenance:

- If the subject was initially randomized to CZP 200mg Q2W and completes the Week 52 visit:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of Week 0 administration of study medication is attributable to CZP 200mg Q2W.
  - Date of Week 50 administration (or if Week 50 injection date is missing, date of last administration) of study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days is attributable to CZP 400mg Q2W.

For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

- If the subject was initially randomized to CZP 200mg Q2W and discontinued prior to the Week 52 visit, use the minimum of the following:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of Week 0 administration of study medication is attributable to CZP 200mg Q2W.
  - For CZP 400mg Q2W, use the minimum of the following:
    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first open-label CZP 400mg Q2W administration of study medication + 1 day

    For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.
- If the subject was initially randomized to CZP 400mg Q2W and completes the Week 52 visit:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of Week 50 administration (or if Week 50 injection is missing, date of last administration) of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days)] is attributable to CZP 400mg Q2W.
  - For subjects who die, this calculation reverts to [(Date of Week 16 administration of study medication – date of first administration of study medication) + (Date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day)] is attributable to CZP 400mg Q2W.
- If the subject was initially randomized to CZP 400mg Q2W and discontinued prior to the Week 52 visit:
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - For CZP 400mg Q2W, use (Date of Week 16 administration of study medication – date of first administration of study medication) + the minimum of the following:
    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first open-label CZP 400mg Q2W administration of study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

- If the subject was not initially randomized to CZP 200mg Q2W or CZP 400mg Q2W and completes the Week 52 visit:
  - Date of Week 16 administration of study medication – date of Week 0 administration of study medication is attributed to the original treatment
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - Date of Week 50 administration (or, if Week 50 injection is missing, date of last administration) of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days is attributed to CZP 400mg Q2W

    For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.
- If the subject was not initially randomized to CZP 200mg Q2W or CZP 400mg Q2W and discontinues prior to the Week 52 visit:
  - Date of Week 16 administration of study medication – date of Week 0 administration of study medication is attributed to the original treatment
  - Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.
  - For CZP 400mg Q2W, use the minimum of the following:
    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days
    (2) Date of last clinical contact – date of first administration of open-label CZP 400mg Q2W study medication + 1 day

    For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

Combined Initial and Maintenance Period

Cohort subjects

Duration of exposure

For subjects who discontinue on/prior to the Week 16 visit:

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

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not up-titrate to CZP 400mg Q2W at Week 16 or at any point during Maintenance:

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

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of study medication + 1 day.

For subjects who do up-titrate to CZP 400mg Q2W during Maintenance:

– Date of first administration of CZP 400mg Q2W study medication – date of first administration of CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.

– Date of last administration of CZP 400mg Q2W study medication – date of first administration of CZP 400mg Q2W study medication + 14 days is attributable to CZP 400mg Q2W.

– Date of last administration of study medication – date of first administration of study medication + 14 days is attributable to "All CZP".

For subjects who die, if date of last administration of study medication + 14 days extends to a date beyond the date of death, then this calculation reverts to date of death – date of first administration of CZP study medication + 1 day.

Number of days a dose was received

For subjects who discontinue on/prior to the Week 16 visit:

– Total number of dose days from Week 0 to last dose received (inclusive).

For subjects who do not up-titrate at Week 16 or at any point during Maintenance:

– Total number of dose days from Week 0 to last dose received (inclusive).

For subjects who do up-titrate to CZP 400mg Q2W during Maintenance:

– Total number of dose days from Week 0 to last dose of CZP 200mg Q2W study medication received (inclusive) is attributable to CZP 200mg Q2W

– Total number of dose days from escape through last dose received is attributable to CZP 400mg Q2W

Patient exposure days at risk

For subjects who discontinue on/prior to the Week 16 visit, use the minimum of the following:

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

– Date of last clinical contact – date of first administration of study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do not up-titrate at Week 16 or at any point during Maintenance, and who complete the Week 52 visit:

– Date of Week 50 administration of study medication – date of first administration of study medication + 70 days

– If the subject is missing their Week 50 injection date, then this calculation reverts to: Date of last administration of study medication – date of first administration of study medication + 70 days.

For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day.

For subjects who do not up-titrate at Week 16 or at any point during Maintenance, and who discontinue prior to the Week 52 visit, use the minimum of the following:

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

– Date of last clinical contact – date of first administration of study medication + 1 day

For subjects who die, this calculation reverts to date of death – date of first administration of study medication + 1 day

For subjects who do up-titrate to CZP 400mg Q2W during Maintenance:

– Subjects who complete the Week 52 visit:

  ◦ Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.

  ◦ Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication + 70 days is attributable to CZP 400mg Q2W.

  For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

– Subjects who discontinue prior to the Week 52 visit:

  ◦ Date of first administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 200mg Q2W study medication is attributable to CZP 200mg Q2W.

  ◦ For CZP 400mg Q2W time at risk, use the minimum of the following:

    (1) Date of last administration of open-label CZP 400mg Q2W study medication – date of first administration of open-label CZP 400mg Q2W study medication + 70 days

    (2) Date of last clinical contact – date of first administration of open-label CZP 400mg Q2W study medication + 1 day

  For subjects who die, this calculation reverts to date of death – date of first administration of open-label CZP 400mg Q2W study medication + 1 day.

10.2 Adverse events

Definitions and Data Handling Conventions

AEs recorded on the Baseline day will be regarded as 'treatment emergent'. AEs occurring either before study drug administration (pre-treatment) or more than 70 days after last study drug administration will not be considered to be treatment emergent (TEAE). If a subject dies during the treatment period (timeframe: first study drug administration to last study drug administration +70 days), then the period for TEAEs will end with the death date. If a subject

has a Safety follow-up visit that extends beyond 70 days after the last study drug administration, then the period for TEAEs for that subject will end at the last study drug administration + 70 days.

Non treatment emergent AEs will only be listed separately.

Only AEs occurred at or prior to the visit of Week 24 will be included in the interim analysis.

Adverse events that occur on the Week 16 visit date will be attributed to the initial randomized treatment. The only exception to this definition is for the following types of events:

- Those which code to a HLT of "Injection Site Reactions"
- Those which have been designated as an Injection Reaction on the AE CRF and do not code to an SOC of "Investigations"
- Those which have been identified as a hypersensitivity reaction or an anaphylactic reaction

When any of these events occur on the Week 16 visit date, the AE will be attributed to the treatment received at Week 16.

In general, AEs will be allocated to the treatment group based on the dose most recently received.

The following rules will be applied to impute partial onset dates for AEs:

If the AE onset date is completely unknown, then use the date of first dose in the Initial Period.

If only the year is specified:

If the year of first dose in the Initial Period is the same as the year of onset, then use the date of first dose in the Initial Period.

If the year of first dose in the Initial Period is not the same as the year of onset, then use January 1 of the year of onset.

If only the month and year are specified:

If the month and year of first dose in the Initial Period is the same as the month and year of onset, then use the date of first dose in the Initial Period.

If the month and year of onset is after the month and year of first dose in the Initial Period and prior to the month and year of first dose in the Maintenance Period, then use the 1st of the month.

If the month and year of first dose in the Maintenance Period is the same as the month and year of onset, then use the date of first dose in the Maintenance Period.

If the month and year of onset is after the month and year of first dose in the Maintenance Period, then use the 1st of the month.

If the intensity of an adverse event is unknown, it is considered as severe.

If the relationship to study drug is missing, it is considered as related.

Subject time at risk represents the time a subject was at risk for having an AE. The definitions for subject time at risk (in days) for the Initial Period, Maintenance Period, and Combined Initial and Maintenance Period are outlined in Section 10.1. These definitions will be used for

exposure-adjusted AE summaries. Selected AE summaries will include the exposure adjusted incidence rate (EAIR) with associated 95% confidence interval and the exposure adjusted event rate (EAER).

For EAIR, the numerator will be the total number of subjects experiencing the AE. The denominator will be 100 subject-years; that is, the total summation of individual subject-years at risk up to the first occurrence of the AE for subjects with that AE, and the total subject-years at risk for those subjects not experiencing that AE, divided by 100. EAIRs will be presented with a 95% exact confidence interval based upon the Chi-Square distribution (Ulm, 1990).

For EAERs, the numerator will be the number of AEs including repeat occurrences in individual subjects; the denominator will be 100 subject-years. That is, the total summation of individual subject-years at risk divided by 100. No confidence interval will be computed for EAER.

Presentation Conventions

The frequency of all TEAEs during the study period will be presented by treatment group and period separately by SOC, High Level Term (HLT), and preferred term (PT). The data will be displayed as number of subjects experiencing the AE, percentage of subjects, and number of AEs, sorted by descending frequencies of PTs in the 'All CZP Subjects' column and ordered alphabetically for SOC, HLT and identical frequencies for PTs.

Tables for the Incidence of TEAEs – Overview and Incidence of TEAEs will be generated by TE-ADA status using the following categories:

1. TEAEs starting before 1st anti-CZP antibody positive
2. TEAE starting on or after 1st anti-CZP antibody positive
3. TEAEs for subjects who are always anti-CZP antibody negative

Each event will be classified according to whether it occurred on or after the first + result, or for a subject that remained negative throughout. Summaries will include the number of AEs, number of subjects with AEs and percentage of subjects with AEs, incidence rate with 95% CI, and exposure-adjusted event rate. For these summaries, a subject's associated time at risk will be split into the time before the first positive result, and on or after the first positive result. If a subject has multiple reports of the same AE (ie, those which code to the same PT) emerging both prior to first TE-ADA positive result and after first TE-ADA positive result, both events will be summarized in the table in the appropriate column.

Tables for the incidence of TEAEs will be generated for Combined Initial and Maintenance Period by maximum ADA titers using the following categories:

- Low: maximum ADA titer <= 1024
- High: maximum ADA titer > 1024
- NA: Since ADA titer for escape subjects is measured only at the time of transition and SFU, AEs emerging after escape transition will be included in "NA".

Since this tabulation covers all subjects assigned to CZP, AEs emerging while on PBO are excluded. Also, in order to include all CZP-treated subjects, subjects in the SS and the CSS will be combined together into a single table.

Finally, AEs of interest (AEOIs) will be evaluated as described below:

- Serious infections, including opportunistic infections. Serious infections will be summarized using the previously described "Any SAE" table. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.
- Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = "Malignant or unspecified tumours (SMQ)" and SMQ = "Malignant tumours (SMQ)", respectively. The SMQ search will include terms in the Scope=Narrow group only. Note that the events include in the "Malignant tumours" table will be a subset of the events included in the "Malignant or unspecified tumours" table.
- Congestive heart failure. These will be manually identified by the study physician from the previously described Any TEAE table. No separate table is planned. In addition, serious cardiovascular events will be presented in a table using UCB-defined search criteria.
- Demyelinating-like disorders. These will be presented in a stand-alone table which is based on the SMQ = "Demyelination". The SMQ search should include all TEAEs which code to a PT included in Scope=Narrow group within the SMQ. TEAEs which code to a PT included in the Scope=Broad group within the SMQ should be excluded from the search.
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = "Haematopoietic cytopenias (SMQ)" in the subset of SAEs. The SMQ search will include terms in the Scope=Narrow and Scope=Broad groups.
- Serious bleeding events. These will be presented in a table using the criteria SMQ = "Haemorrhage terms (excl laboratory terms) (SMQ)" in the subset of SAEs.
- Lupus and lupus-like illness. These will be manually identified by the study physician from the previously described Any TEAE table. No separate table is planned.
- Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme). These will be manually identified by the study physician from the previously described Any SAE table. No separate table is planned.

The tables for the AEOIs will include the incidence rate with associated 95% confidence interval, and the exposure adjusted event rate.

Will also be summarized:

- Hepatic events. They will be identified using the following 5 SMQs: "Cholestasis and jaundice of hepatic origin (SMQ)"; "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)"; "Hepatitis, noninfectious (SMQ)"; "Liver-related investigations, signs and symptoms (SMQ)"; and "Liver-related coagulation and bleeding disturbances (SMQ)".
- Hypersensitivity reactions and anaphylactic reactions. Hypersensitivity reactions will be identified as TEAEs that emerge on the same day or within one day after a study medication injection reaction was received which code to the following 10 PTs: "Administration site hypersensitivity"; "Documented hypersensitivity to administered product"; "Drug hypersensitivity"; "Hypersensitivity"; "Hypersensitivity vasculitis"; "Infusion site hypersensitivity"; "Injection site hypersensitivity"; "Medical device

hypersensitivity"; "Type II hypersensitivity"; "Type IV hypersensitivity reaction". Anaphylactic reactions will be identified using UCB-defined search criteria.

- Major Cardiovascular Events (MACEs). They will be identified using the following SMQs: "Central nervous system haemorrages and cerebrovascular conditions (SMQ)", which includes the 3 following sub SMQs: "Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)", "Haemorrhagic central nervous system vascular conditions (SMQ)", "Ischaemic central nervous system vascular conditions (SMQ)" except events coding to PT "Transient ischaemic attack". All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to PT "Chest Pain" or "Chest discomfort" and all serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders" as Primary SOC will be included.

AE Summaries by Period

All of the presentations described above will be presented for the Initial Period. Subsets of the presentations described above will be presented for the Maintenance Period and for the Combined Initial and Maintenance Period. Details for these summaries are described below.

Initial Period

Summaries for the Initial Period will be presented by randomized treatment group (PBO, CZP 200mg Q2W, CZP 400mg Q2W, All CZP) based on the SS, PsA Set and the CSS. For these summaries, treatment-emergence is defined as follows:

- For subjects who complete the Week 16 visit and continue to the Maintenance Period, all AEs which started on or after the date of first dose of study medication and on or prior to the date of the Week 16 administration of study medication will be considered a TEAE for these summaries. The only exception to this rule is for the following types of events:
  - Those which code to a HLT of "Injection Site Reactions"
  - Those which have been designated as an Injection Reaction on the AE CRF and do not code to an SOC of "Investigations"
  - Those which have been identified as a hypersensitivity reaction or an anaphylactic reaction

  When any of these events occur on the date of treatment switch at Week 16, the AE will be attributed to the treatment initiated at Week 16.
- For subjects who discontinue on or prior to the Week 16 visit, all AEs which started on or after the first dose of study medication and on or prior to the date of last administration of study medication + 70 days will be considered a TEAE for the analysis summaries.
- For subjects who die prior to the Week 16 visit, all AEs which started on or after the first dose of study medication and prior to or on the date of death will be considered a TEAE for these summaries.

The following AE summaries will be presented:

- Incidence of TEAEs – Overview
- Incidence of TEAEs by TE-ADA status – Overview
- Incidence of TEAEs by TE-ADA status (Includes EAIR and EAER)

- Incidence of TEAEs (includes EAIR and EAER)
- Incidence of Serious TEAEs (includes EAIR and EAER)
- Incidence of TEAEs Resulting in Permanent Discontinuation of Study Drug
- Incidence of TEAEs leading to death
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs by Maximum Relationship
- Incidence of Serious TEAEs by Maximum Relationship
- Incidence of Non-serious TEAEs by Maximum Relationship
- Incidence of TEAEs on or above Reporting Threshold of 5% (not for CSS)
- Incidence of Non-serious TEAEs on or above Reporting Threshold of 5% (not for CSS)
- Incidence of Non-serious TEAEs on or above Reporting Threshold of 5% by Maximum Relationship (not for CSS)
- All AEOI tables

Maintenance Period

The incidence of TEAEs Overview table (open-label) will be provided by treatment group (CZP 200mg Q2W, CZP 400mg Q2W, All CZP) based on the SS. The following AE summaries will be produced considering just those AEs which emerged during the Maintenance Period while on open-label (escape) treatment using the SS and PsAS:

- Incidence of TEAEs – Overview
- Incidence of TEAEs (includes EAIR and EAER)
- Incidence of Serious TEAEs (includes EAIR and EAER)
- Incidence of TEAEs Resulting in Permanent Discontinuation of Study Drug
- Incidence of TEAEs leading to death
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs by Maximum Relationship
- Incidence of TEAEs on or above Reporting Threshold of 5%

Additionally, a listing of TEAEs emerging while on escape treatment will be produced.

Combined Initial and Maintenance Period

Summaries for the Combined Initial and Maintenance Period will be presented by safety treatment group based on the SS, PsAS, and CSS. For these summaries, treatment-emergence is defined as follows:

- For subjects who complete the Week 24 visit, all AEs which started on or after the date of first dose of study medication and on or prior to the date of the Week 24 administration of study medication will be considered a TEAE for the interim analysis summaries.
- If a subject discontinues prior to the Week 24 visit and has a Safety follow-up visit that extends beyond 24 weeks from the first study drug administration (ie, what would have been the Week 24 visit), then the period for TEAEs for that subject will end at 24 weeks

(160 days) from the first study drug administration for the interim analysis. Any TEAEs collected at the Safety follow-up visit occurring after the 24 week timepoint will be captured in the Final Clinical Study Report (CSR). This allows for a maximum treatment period of 24 weeks for each subject in this interim analysis.

- For subjects who complete the Week 52 visit, all AEs which started on or after the date of first dose of study medication and on or prior to the date of Week 50 administration of study medication + 70 days will be considered a TEAE for the final analysis summaries.
- For subjects who discontinue prior to the Week 52 visit, all AEs which started on or after the first dose of study medication and on or prior to the date of last administration of study medication + 70 days will be considered a TEAE for the final analysis summaries.
- For subjects who die prior to the Week 24/52 visit, all AEs which started on or after the first dose of study medication and prior to or on the date of death will be considered a TEAE for the interim/final analysis summaries.

The following AE summaries will be produced for the Combined Initial and Maintenance Periods considering just those AEs which emerged while on blinded or open-label treatment using the SS, PsAS and CSS:

- Incidence of TEAEs – Overview
- Incidence of TEAEs by TE-ADA status – Overview
- Incidence of TEAEs by TE-ADA status (Includes EAIR and EAER)
- Incidence of TEAEs by Maximum ADA Titer (Safety Set (Excluding PBO treatment group) and Cohort Safety Set combined)
- Incidence of TEAEs (includes EAIR and EAER)
- Incidence of Serious TEAEs (includes EAIR and EAER)
- Incidence of TEAEs Resulting in Permanent Discontinuation of Study Drug
- Incidence of TEAEs leading to death
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs by Maximum Relationship
- Incidence of Serious TEAEs by Maximum Relationship
- Incidence of Non-serious TEAEs by Maximum Relationship
- Incidence of TEAEs on or above Reporting Threshold of 5% (not for CSS)
- Incidence of Non-serious TEAEs on or above Reporting Threshold of 5% (not for CSS)
- Incidence of Non-serious TEAEs on or above Reporting Threshold of 5% by Maximum Relationship (not for CSS)
- All AEOI tables

The following AE summaries will be produced for the Combined Initial and Maintenance Periods considering AEs which emerged while on blinded treatment only for the SS, PsAS:

- Incidence of TEAEs – Overview
- Incidence of TEAEs (includes EAIR and EAER)

- Incidence of Serious TEAEs (includes EAIR and EAER)
- Incidence of TEAEs Resulting in Permanent Discontinuation of Study Drug

10.3 Clinical laboratory evaluations

Definitions and Data Handling Conventions

The following table indicates the laboratory data that will be collected. Note that hematology and chemistry data will be summarized in tables. Urinalysis data will be listed only.

Table 10–1: Laboratory parameters to be collected

Hematology	Chemistry	Urinalysis
Basophils	Calcium	Albumin
Eosinophils	Chloride	Bacteria
Lymphocytes	C-reactive protein	Crystals
Atypical lymphocytes	Magnesium	Glucose
Monocytes	Potassium	pH
Neutrophils	Sodium	Red blood cells (RBC)
Hematocrit	Glucose	White blood cells (WBC)
Hemoglobin	Urea nitrogen	Urine dipstick for pregnancy testing[a]
Mean corpuscular hemoglobin (MCH)	Creatinine	
Mean corpuscular hemoglobin concentration (MCHC)	Alkaline phosphatase (ALP)	
Mean corpuscular volume (MCV)	Aspartate aminotransferase (AST)	
Platelet count	Alanine aminotransferase (ALT)	
RBC count	Gamma glutamyl transferase (GGT)	
WBC count	Bilirubin	
	Lactate dehydrogenase (LDH)	
	Cholesterol	
	Albumin	
	1,3 Beta-D-glucan	
	KL-6	
	Hepatitis B surface antigen[b]	
	Hepatitis B core antibody[b,c]	
	Hepatitis B surface antibody[b,c]	

Table 10–1: Laboratory parameters to be collected

Hematology	Chemistry	Urinalysis
	Hepatitis type B virus DNA[c]	
	Hepatitis type C virus antibody[b]	
	Human immunodeficiency virus antigen[b]	
	Human immunodeficiency virus antibody[b]	
	T-cell lymphotropic virus type-1 antibody[b]	
	Serum pregnancy testing[a]	

[a] Pregnancy testing will consist of serum testing at Screening. The pregnancy test will be urine at all other visits.
[b] Performed at Screening only
[c] If the subject is either HBs antibody-positive or HBc antibody-positive at Screening, quantitative measurement of HBV-DNA should be performed every 4 weeks from Baseline to Week 52 and at SFU.

The following parameters will not be included in the chemistry tables:

- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis B surface antibody
- Hepatitis B virus DNA
- Hepatitis C virus antibody
- Human immunodeficiency virus antigen
- Human immunodeficiency virus antibody
- T-cell lymphotropic virus type-1 antibody
- Serum pregnancy testing

Values by visit will only be listed.

Markedly abnormal laboratory values will be defined as those categorized as Grade 3 or higher based on the Rheumatology Common Toxicity Criteria (RCTC) v2.0 (Woodworth et al, 2007). Definitions of markedly abnormal values for hematology and chemistry using the Grade 3 cut points are provided below

Table 10–2: Definitions of markedly abnormal hematology values

Parameter (SI units)	Markedly abnormal low	Markedly abnormal high
Hemoglobin (g/L)	< Lower Limit of Normal (LLN) AND decrease from Baseline >20	Not applicable
Hemoglobin (g/L)	<80	Not applicable
Leukocytes (total x 1000)	<2.0	Not applicable
Lymphocytes (x 1000) [a]	<0.5	Not applicable

Table 10–2: Definitions of markedly abnormal hematology values

Parameter (SI units)	Markedly abnormal low	Markedly abnormal high
Neutrophils (x 1000)	<1.0	Not applicable
Platelets (x 1000)	<50	Not applicable

[a] For lymphocytes, the Grade 3 CTCAE cut point is used as the RCTC Grade 3 cut point (<1.0) is higher than the lower limit of normal (0.8) specified by the lab.

Table 10–3: Definitions of markedly abnormal chemistry values

Parameter (SI units)	Markedly abnormal low	Markedly abnormal high
ALT (U/L)	Not applicable	>3x ULN
AST (U/L)	Not applicable	>3x ULN
Calcium (mmol/L)	<1.75	>3.125
CPK (U/L)	Not applicable	>4x ULN
Glucose (mmol/L)	<2.22	>13.89
Potassium (mmol/L)	<3.0	>6.4
Sodium (mmol/L)	<125	Not applicable
Total bilirubin (μmol/L)	Not applicable	≥2x ULN

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. For tables where multiple measurements over a period of time are considered (as in shift tables), unscheduled and repeat visits will be considered as long as they were collected in the period being summarized. All laboratory summaries will be presented in SI units and will be based on observed case values. In the case where laboratory values are below the lower limit of quantification, then these will be set to the lower limit of quantification divided by 2 for the purpose of summarizing the data.

The criteria for meeting Hy's Law are defined as follows:

- ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP.

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST at the same visit. For example, a subject 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.

Other liver function test elevations that are of interest for summary purposes are:

- 3x, 5x, 8x ULN elevations of AST,
- 3x, 5x, 8x ULN elevations of ALT,
- 3x, 5x, 8x ULN elevations of either AST or ALT,
- 1x, 1.5x ULN elevations of Bilirubin
- 3x ALP

For determining cases of Hy's Law and other liver function test elevations, only post-Baseline assessments are considered. Pre-treatment and Safety Follow-up assessments are excluded. Additionally, assessments collected more than 70 days after the last dose of study treatment are excluded.

Lab Data Summary by Period

Initial Period

All summaries for the Initial Period will be presented by treatment group for the SS and the CSS.

Hematology and chemistry absolute and change from Baseline values will be summarized by visit using descriptive statistics for continuous data. In addition, the summaries will include descriptive statistics within the Initial Period for the end of treatment, minimum post-Baseline, and maximum post-Baseline values.

Shift from Baseline tables for lab values based on the normal range will be presented within the Initial Period for the end of treatment, minimum post-Baseline and maximum post-Baseline values. The shift categories will be low, normal, high, and missing.

The number and percent of subjects with markedly abnormal (≥grade 3 by CTCAE) hematology or chemistry values will be summarized by visit and for any visit during the Initial Period. For the "any visit" summary, only values while on study treatment will be considered, meaning that the Baseline measurement will not be considered.

Shift from Baseline tables for lab values based on the markedly abnormal lab values will be presented within the Initial Period for the end of treatment, minimum post-Baseline, and maximum post-Baseline. The shift categories will be markedly abnormal, not markedly abnormal, and missing.

The number and percent of subjects meeting Hy's law criteria and other liver function test elevations specified above at any visit while on study treatment (i.e., Baseline excluded) during the Initial Period will be summarized.

Combined Initial and Maintenance Period

The summaries described above for the Initial Period will be repeated for the Combined Initial and Maintenance Period and will be presented based on the SS and CSS. For the summaries based on the SS, the tables that are produced will include data while on either blinded or open-label treatment.

For the markedly abnormal values summary by visit, the percentage will be based on the number of subjects with observed values at the given visit. Therefore, the denominator will vary based on the visit. For the "any visit" summary, this will be based on all observed values.

Shift from Baseline tables for markedly abnormal lab values will be presented for the Combined Initial and Maintenance Period relative to the end of treatment, minimum post-Baseline, and maximum post-Baseline values. The shift categories will be markedly abnormal, not markedly abnormal, and missing.

If a subject switches blinded CZP dose from Initial to Maintenance Period, the minimum post-baseline value, the maximum post-baseline value and the end of treatment value will be determined for each respective dose received. For the summarization of "All CZP", the minimum and maximum post-baseline value will be determined considering values reported

while on either CZP dose; the end of treatment value will reflect the values reported while on the last CZP dose received during the study.

The shift table will present shifts by treatment group from Baseline (last observation before Week 0; regardless of which study treatment was administered at Week 0) to post-Baseline minimum, maximum and end of treatment while on treatment summarized. Values observed during blinded and open-label are included.

The number and percent of subjects meeting Hy's law criteria and other liver function test elevations specified above at any visit while on blinded or open-label study treatment (ie, Baseline excluded) during the Combined Initial and Maintenance Period will be summarized.

10.4 Vital signs, physical findings, and others related to safety

10.4.1 Vital signs

Definitions and Data Handling Conventions

All summaries will be based on observed case values. For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings.

In the case that vital signs are collected one or more days following the scheduled visit date, in which the drug was administered, these vital signs results will not be summarized as part of that visit (for by-visit presentations). However, these vital signs results will be considered for tables where multiple measurements over a period of time are considered (as in shift tables) so long as they are in the appropriate period being summarized.

Definitions for the normal range for blood pressure values are given in the table below.

Table 10–4: Definitions of normal range for blood pressure values

Parameter (unit)	Low	High
Systolic blood pressure (mmHg)	<90	>140
Diastolic blood pressure (mmHg)	<60	>90

Definitions of markedly abnormal values for systolic and diastolic blood pressure are given in the table below.

Table 10–5: Definitions of markedly abnormal blood pressure values

Parameter (unit)	Markedly Abnormal Low	Markedly Abnormal High
Systolic blood pressure (mmHg)	<90 and a decrease from Baseline of ≥20	>180 and an increase from Baseline of ≥20
Diastolic blood pressure (mmHg)	<50 and a decrease from Baseline of ≥15	>105 and an increase from Baseline of ≥15

Data Summary by Period

Initial Period

All summaries for the Initial Period will be presented by treatment group for the SS and CSS.

Absolute and change from Baseline blood pressure values will be summarized by visit using descriptive statistics for continuous data. Weight will be summarized in a similar manner.

Shift from Baseline tables for blood pressure values based on the normal range will be presented within the Initial Period for the end of treatment, minimum post-Baseline and maximum post-Baseline values. The shift categories will be low, normal, high, and missing.

Shift from Baseline tables for blood pressure values based on the markedly abnormal blood pressure values will be presented within the Initial Period for the end of treatment, minimum post-Baseline, and maximum post-Baseline. The shift categories will be markedly abnormal, not markedly abnormal, and missing.

Combined Initial and Maintenance Period

The change from Baseline summaries described above for the Initial Period will be repeated for the Combined Initial and Maintenance Period and will be presented based on the SS and on CSS. For the summaries based on the SS, the tables that are produced will include data while on either blinded or open-label treatment.

Shift from Baseline tables for blood pressure values based on the normal range will be presented within the combined Initial and Maintenance Period for the end of treatment, minimum post-Baseline and maximum post-Baseline values. The shift categories will be low, normal, high, and missing. If a subject switches blinded CZP dose from Initial to Maintenance Period, the minimum post-baseline value, the maximum post-baseline value and the final end of treatment will be determined for each respective dose received. For the summarization of "All CZP", the minimum and maximum post-baseline value will be determined considering values reported while on either CZP dose; the final end of treatment value will reflect the values reported while on the last CZP dose received during the study.

The shift table will present shifts by treatment group from Baseline (last observation before Week 0; regardless of which study treatment was administered at Week 0) to post-Baseline minimum, maximum and end of treatment while on treatment summarized. Values observed during blinded and open-label are included.

Shift from Baseline tables for blood pressure values based on the markedly abnormal blood pressure values will be presented within the combined Initial and Maintenance Period for the end of treatment, minimum post-Baseline, and maximum post-Baseline. The shift categories will be markedly abnormal, not markedly abnormal, and missing.

10.4.2 Physical examination

The Investigator will conduct a complete physical examination in all subjects at Screening, at Baseline, at Week 16, at Week 24, at Week 52 and at SFU Visit. The physical examination will cover the following: general appearance, head, ears, eyes, nose, throat, hair, skin, respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, neurological, and mental status. All physical examination data will be listed; clinically relevant changes during the study will be recorded as AEs.

In addition, TB signs and symptoms will be assessed. A listing of these data will be provided including abnormalities and their classification if clinically meaningful or not.

10.4.3 12-lead electrocardiogram

A 12-lead standard electrocardiogram (ECG) will be performed at Screening, Week 24 and Week 52.

Combined Initial and Maintenance Period

Descriptive statistics will be tabulated for the following ECG variables (absolute values and change from baseline) by visit: Heart rate (HR), PQ/PR-interval, QRS-duration, QT-interval,

QTcB-interval. The results will be tabulated based on subjects in the SS and CSS considering data collected while on either blinded or open-label treatment.

Additionally, a shift table will be provided for the number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant ECG results from Screening to each time point considering data collected while on either blinded or open-label treatment (for the SS) and for all subjects in the CSS.

A subject data listing of all 12-lead ECG data will be provided.

10.4.4 Chest x-ray for TB

A chest x-ray must be performed in the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. Further chest x-rays will be performed at Week 12, Week 24 and Week 52. Any new clinically significant findings must be documented and classified as normal, abnormal and not clinically significant or abnormal and clinically significant. Clinically relevant changes during the study will be recorded as AEs.

A shift table will be provided for the number and percentage of subjects with normal, abnormal and not clinically significant and abnormal and clinically significant results from Screening to each time point during Initial and Maintenance Period, considering data collected while on either blinded or open-label treatment (for the SS) and for all subjects in the CSS.

A subject data listing of chest x-ray results will be provided.

10.4.5 Interferon-gamma release assay (IGRA) testing for TB

All subjects will have IGRA testing conducted at Screening, Week 24 and Week 52. Results from this tuberculosis test will be reported as positive, negative, or indeterminate. A listing will be provided for both the SS and CSS.

10.4.6 Subject questionnaire for TB

The questionnaire “Evaluation of signs and symptoms of tuberculosis” will be used as a source document and will assist with the identification of subjects who may require therapy for TB. The results will not be included in the database. Therefore no analysis of the questionnaire results will be performed.

10.4.7 Pregnancy testing

Pregnancy testing will consist of serum testing at Screening and urine testing at all other applicable visits. The results of the pregnancy test will be listed.

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12 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN

12.1 Amendment 1 – Summary of Changes

In Section 4.5 the figure to present the fixed sequence testing procedure has been updated and the text has been adapted accordingly to be in conjunction with the updated figure.

Section 6.2 was updated to correct the DAS28 (CRP) categorization.

Section 8.3.1 was updated to specify the by treatment group for Maintenance Period tables.

Section 8.3.2 was updated to specify the by treatment group for Maintenance Period tables.

Section 8.3.9 was updated to add the ACR20, 50, 70 response criteria analysis based on PsA Set.

12.2 Amendment 2 – Summary of Changes

In General, typos throughout the whole document have been corrected and hyperlinks to sections also have been updated. The format has been improved to get better readability.

SAP Amendment 2 does not interfere with analyses for Interim Analysis. Changes which are made referring to Interim Analysis where already performed like this in the Interim Analysis.

In Section 2.2.3.1 other efficacy variables for the escape population have been added: Change from Baseline in Itch Numeric Rating Scale, ACR20/50/70 response criteria and all ACR core components, change from Baseline in DAS28(CRP) for subjects with PsA at Baseline and change from Baseline in mNAPSI for subjects with nail disease at Baseline.

In Section 3.1 it has been clarified that the earlier visit will be flagged to have the minimum/maximum post-baseline visit, in the case where the minimum/maximum values is observed at multiple visits.

Section 3.2.4 was updated to correct the early withdrawal visit re-mapping. For re-mapping, no scheduled time windows will be checked, but the EWD will only mapped to the next

scheduled visit following the last observed visit. For PK and anti-CZP antibodies, no re-mapping is done.

In Section 3.5.6 the definition for the Pharmacokinetics Per-Protocol Set has been adapted to only check for at least 1 quantifiable CZP plasma concentration while receiving blinded treatment.

In Section 3.5.9 the BM RS has been removed, because it is not needed and BM NAPSI set has been included in the list of blinded maintenance analysis sets. Moreover, the blinded maintenance set is made applicable for the final analysis as well.

Section 3.5.10 introduces the escape maintenance set, which is needed for the analyses planned showing only data assessed after escape visit.

Section 3.5.16 and Section 3.5.17 have been exchanged, because consistently, the SAP text and analysis outputs present EPS results first, before GPPS.

In Section 3.6 the introduction for the treatment assignments and treatment groups have been corrected.

In subsection 3.6.1, especially the treatment groups for the blinded maintenance period and the escape maintenance period for efficacy have been clarified. Additionally, the escape visit itself has been clearly assigned to applicable periods.

Subsection 3.6.2 was updated for cohort treatment groups. A definition was added to clarify, when a subject is assigned to treatment group CZP 200mg Q2W/CZP 400mg Q2W.

In Section 4.1 it has been clarified that the adjustments for covariates are also applicable to secondary and other key efficacy endpoints.

Section 4.2 has been updated for the imputation of missing data for escape subjects (for tables by blinded maintenance treatment group and for tables by escape maintenance treatment group). A general description of NRI imputation and LOCF has been added.

In Section 6, the analysis sets for demographics have been updated.

In Section 6.2 the definition for duration of disease (years) has been clarified and the variable prior systemic treatment for PsA has been added (any systemic treatment for PSO has been corrected at the same time). The derivation of presence of concomitant PsA at Baseline has been updated.

In Section 8.1.2 the procedure, how to handle non-convergence in the logistic regression model has been updated to first using exact logistic regression and second to drop the covariate prior biologic exposure. This has been already described like this in the following of this section like this and is now harmonized.

Also, in Section 8.1.2 it has been changed to present actual observed data and (exact) logistic regression results of the observed data, if all MCMC imputed datasets are exactly the same. Only one MCMC record will be used for analysis then.

Section 8.1.3 and 8.2 have been updated, so that DAS28(CRP) is no subgroup for subgroup analyses anymore.

In Table 8-3 in Section 8.3 the escape arm population has been added for the change from baseline in Itch Numeric Rating Scale. Moreover, the absolute and percent change from baseline in BSA affected by PSO are presented for the Initial and Maintenance Period instead for Initial only.

Section 8.3.1 received an update to clearly state what has been done for interim analysis and what will be done for final analysis. The main point is how to incorporate data of escapers. Additionally, it has been clarified that for the responder rate estimation in the maintenance period, no regression models will be calculated anymore but simple proportions only. Additional escape arm analyses and analyses for combined initial and maintenance period have been described.

Section 8.3.2 has been updated according to the updates in Section 8.3.1 for PGA instead of PASI response.

In Section 8.3.7 it has been clarified that no percent changes from baseline will be summarized for DLQI. Additionally, the ANCOVA analysis by visit to calculate adjusted mean changes for the Initial Period is described. DLQI analyses will also be performed on CFAS. The treatment comparisons in maintenance period are not applicable.

In Section 8.3.9 it has been added that line plots for ACR20/50/70 response rates will be produced. Moreover, tables will also be provided for the escape maintenance period.

For the section referring to ACR20/50/70 core components, Section 8.3.10, Section 8.3.11, Section 8.3.12, Section 8.3.13 and Section 8.3.14, it has been clarified that the analyses are according to Section 8.3.9.

In Section 8.3.15, the correct subset of joints for DAS28(CRP) have been listed (see Protocol Section 9.7.3). The LOCF imputation for DAS28(CRP) has been concretized.

Section 8.3.17 was updated to mention with which CGI-I category missing data will be imputed for NRI.

For Section 8.3.18 the category for NRI imputation has been updated for the Global Improvement Score.

The complete Section 9 was updated, because analyses have been added for relationship between immunogenicity and pharmacokinetics, efficacy and safety. In final analysis, analyses by treatment-emergent ADA status will be substituted by analyses for anti-CZP antibody maximum titer categories. Treatment groups to present in outputs have been clarified.

The Section 10.1 was updated to correct inconsistencies in calculation the extent of exposure. Section 10.1.1 is the section previously described for the interim analysis. The new calculation rules for the final analysis are in Section 10.1.2.

In Section 10.2 it has been clarified which AE tables will be presented for the Initial Period, for the Maintenance Period (based on escape data only) and for Combined Initial and Maintenance Period (based on blinded data only and based on either blinded or escape data).

In Section 10.3 some laboratory parameters labels are harmonized. Serum pregnancy testing is added to the list of parameters which are not included in chemistry tables. No table summarizing Psoriasis Baseline Characteristics is provided. For the Hy's Law summary, additional liver function test elevations are added as of interest in Section 10.3. Moreover, Combined Initial and Maintenance Period analyses are updated. It has been clarified how to handle treatment switcher at Week 16 in shift tables.

In Section 10.4 and corresponding subsections, Maintenance Period analyses have been added for Vital Signs and 12-lead electrocardiogram. Analyses for Combined Initial and Maintenance Period have been concretized. For physical examination, chest x-ray for TB and interferon-gamma release assay for TB the analysis sets are specified in more detail.

13 APPENDICES

13.1 Schedule of study assessments

A schedule of study assessments is presented Table 13–1.

Table 13–1: Schedule of study assessments

Visit/ Week (Wk)			Treatment Period																										SFU Visit
Protocol Activity	V1/Screening	V2/Baseline	V3/Wk 2	V4/Wk 4	V5/Wk 6	V6/Wk 8	V7/Wk 10	V8/Wk 12	V9/Wk14	V10/Wk16	V11/Wk 18	V12/Wk 20	V13/Wk 22	V14/Wk 24	V15/Wk 26	V16/Wk 28	V17/Wk 30	V18/Wk 32	V19/Wk 34	V20/Wk 36	V21/Wk 38	V22/Wk 40	V23/Wk42	V24/Wk 44	V25/Wk 46	V26/Wk 48	V27/Wk 50	Wk 52/ EWD	
Inclusion/exclusion	X	X																											
Informed consent	X																												
Demographic data	X																												
Psoriasis history	X																												
Significant past medical history and concomitant diseases	X																												
Blood pressure	X	X	X	X		X		X		X		X		X		X		X				X						X	X
Temperature, pulse	X																												
Height	X																												
Weight	X	X								X															X		X		
12-lead ECG	X													X													X		
Hematology/ biochemistry	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X	X
Beta-D-glucan	X			X				X						X														X	
Sialylated carbohydrate antigen KL-6	X													X														X	
Urine[a]	X	X	X	X	X	X	X	X	X	X				X				X				X				X		X	X
Pregnancy testing[b]	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X
Hepatitis B and C testing, HIV testing; HTLV-1 testing[c]	X																												
Plasma for CZP concentration and anti-CZP antibodies[d]		X	X	X	X	X		X		X				X				X				X						X	X

Table 12–1: Schedule of study assessments

Visit/ Week (Wk) / Protocol Activity	V1/Screening	V2/Baseline	Treatment Period																										SFU Visit
			V3/Wk 2	V4/Wk 4	V5/Wk 6	V6/Wk 8	V7/Wk 10	V8/Wk 12	V9/Wk14	V10/Wk16	V11/Wk 18	V12/Wk 20	V13/Wk 22	V14/Wk 24	V15/Wk 26	V16/Wk 28	V17/Wk 30	V18/Wk 32	V19/Wk 34	V20/Wk 36	V21/Wk 38	V22/Wk 40	V23/Wk42	V24/Wk 44	V25/Wk 46	V26/Wk 48	V27/Wk 50	Wk 52/ EWD	
Physical exam[e]	X	X								X				X														X	X
Chest x-ray	X[t]							X						X														X	
IGRA	X													X														X	
TB Questionnaire	X	X						X		X				X				X										X	
PASI[g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
PGA[g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Itch Numeric Rating Scale		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
BSA affected by PSO[g]	X	X								X																		X	
DLQI		X	X			X		X		X				X				X				X				X		X	
mNAPSI[h]		X	X			X		X		X				X				X				X				X		X	
Subject PsA assessments[i]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Physician PsA assessments[j]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Pustular and erythrodermic PSO assessments[g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CZP or PBO administration[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

BSA=body surface area; CGI-I= Clinical Global Impression-Improvement; CZP=certolizumab pegol; DLQI=Dermatology Life Quality Index; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EWD=Early Withdrawal Visit; HAQ-DI=Health Assessment Questionnaire-Disability Index; HBV=hepatitis Type B virus; HIV=human immunodeficiency virus; HTLV-1=human T-cell lymphotropic virus type-1; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; JDA=Japanese Dermatological Association; mNAPSI=modified Nail Psoriasis Severity Index;
PASI=Psoriasis Area and Severity Index; PBO=placebo; PGA=Physician's Global Assessment; PhGADA=Physician's Global Assessment of Disease Activity;

PGADA=Patien's Global Assessment of Disease Activity; PsA=psoriatic arthritis; PSO=psoriasis; SFU=Safety Follow-Up; TB=tuberculosis; V=visit; VAS=visual analog scale; WBC=white blood cells; Wk=week

Note: The Screening Visit should occur between Week -5 and Week -2. The period between the Screening and Baseline Visits should not exceed 5 weeks.

[a] Urine dipstick to be performed every 2 months after Week 16. If blood or WBC are present, a microscopic examination should be performed.

[b] Pregnancy testing will be serum testing at Screening, and urine at all other visits.

[c] HBV DNA to be performed at Screening. If the subject is either hepatitis B surface antibody-positive or hepatitis B core antibody-positive at Screening, quantitative measurement of HBV-DNA should be performed every 4 weeks from Baseline to Week 52 and at SFU.

[d] Subjects who are on escape treatments should have samples taken for plasma CZP concentration and anti-CZP antibodies at the time of escape from double-blind treatment and 10 weeks after the final study drug administration.

[e] Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.

[f] Screening chest x-ray must have been performed within 3 months prior to the Screening Visit.

[g] PASI, PGA, and BSA will not be performed for subjects with generalized pustular PSO. The Global Improvement Score, JDA Severity Index, and CGI-I will be performed for subjects with generalized pustular PSO. For subjects with erythrodermic PSO, the CGI-I will be performed. Note: The CGI-I and Global Improvement Score will not be performed at Screening or Baseline.

[h] For subjects with psoriatic nail disease only

[i] For subjects with PsA: HAQ-DI, Patient's Assessment of Arthritis Pain (VAS), and PGADA (VAS)

[j] For subjects with PsA: swollen and tender joint counts and PhGADA (VAS)

[k] Adverse events should be reported only if they occur after signing the Informed Consent form.

[l] IMP administration of the IMP will occur after all other visit assessments have been completed.

14 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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