

STATISTICAL ANALYSIS PLAN

Study: RA0098
Product: Certolizumab Pegol

A Multicenter, Open-Label Study to Evaluate the Safe and Effective Use of an Electro-Mechanical Injection Device (E-Device) for the Subcutaneous Self-Injection of Certolizumab Pegol Solution by Subjects with Moderate to Severe Active Rheumatoid Arthritis, Active Ankylosing Spondylitis, Active Psoriatic Arthritis, or Moderately to Severely Active Crohn's Disease.

SAP/Amendment Number **Date**
Final SAP 1.0 17 Nov 2017

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LIST OF ABBREVIATIONS

ADE	adverse device effect
AE	adverse event
ASI	Assessment of Self-Injection
BP	Blood Pressure
CD	Crohn's disease
CI	Confidence interval
CZP	Certolizumab pegol
ECG	electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Provider
IMP	Investigational Medicinal Product
IXRS	Interactive Response Technology
PFS	Pre-Filled Syringe
PsA	Psoriatic Arthritis
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RA	Rheumatoid Arthritis
RR	Respiratory Rate
PT	Preferred Term
SADE	Serious Adverse Device Effect

SAE	Serious Adverse Event
SC	Subcutaneous
SOP	Standard Operating Procedure
SS	Safety Set
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Events
VAS	Visual Analog Scale

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1 INTRODUCTION

This statistical analysis plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report (CSR). The SAP is based on the following study document: Protocol Amendment 2 29 Sep 2017.

2 PROTOCOL SUMMARY

RA0098 is a multicenter, open-label, Phase 3 study of the e-Device in US subjects with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), or Crohn's disease (CD).

The e-Device offers improved convenience with an enhanced, reusable electromechanical injector that provides full electronic management of the injection process including subject instructions and warnings via a graphical user interface, an electronic log of the injection history, and the speed of injection. The e-Device uses a disposable single-use certolizumab pegol (CZP) cassette/dose dispensing cartridge (henceforth referred to as CZP-cassette) which houses a (market authorized) pre-filled syringe (PFS) containing CZP 200mg. The CZP-cassette is needle-safe (ie, automatic needle retraction to prevent needle-stick injury), and, once loaded into the e-Device, is electronically recognized (ie, expiry date, drug identity, and use status) by the e-Device. The e-Device and CZP-cassette together provide automatic needle insertion, dose delivery, needle retraction, and adjustable injection speed. They also provide a manual voluntary injection pause and resumption for additional control as well as an automatic stop (with needle retraction) should the e-Device lose contact with the skin during an injection to prevent needle stick injury and to minimize the loss of CZP. A production version of the e-Device will be utilized for this study.

The purpose of this study is to determine whether the e-Device can be used safely and effectively for self-injection by subjects with RA, AS, PsA, or CD after being trained on proper self-injection technique. All eligible subjects should be currently treated with commercial CZP. Eligible subjects with RA, PsA, or AS will perform CZP self-administration a 2 week (Q2W) or 4 week (Q4W) dosing schedule. Eligible subjects with CD will perform CZP self-administration on a Q4W dosing schedule. As the dosing schedule groups (Q2W vs Q4W) are different regarding number of injections (1 CZP injection for Q2W vs 2 CZP injections per administration for Q4W) and study treatment period (2 weeks vs 4 weeks), these 2 subject populations will be evaluated separately. For simplicity and where appropriate, the RA, AS, and PsA subjects on the Q2W dosing regimen will be called the Q2W group, and the RA, AS, PsA, and CD subjects on the Q4W dosing regimen will be called the Q4W group.

The primary variable is the proportion (%) of subjects able to self-administer safe and effective injections using the e-Device at Visit 2. Safe and effective self-injection will be evaluated by the healthcare provider (HCP) and is defined as:

- Complete Dose Delivery: Subject self-injected the complete dose of CZP as confirmed by a visual inspection of the CZP-cassette(s) which shows the container PFS to be empty and

- No adverse events (AE) related to the use of the e-Device (adverse device effects [ADE]) that would preclude continued use of the e-Device for self-injection

Approximately 80 subjects ≥ 18 years of age who are currently being treated with commercial CZP, are self-injecting with the PFS, and are on a stable dosing regimen for at least 3 months will be screened in order to have at least 60 subjects use the e-Device at Visit 1. The 60 subjects using the e-Device at Visit 1 will be composed of a minimum of 15 subjects in each of the dosing groups (Q2W vs Q4W) with a minimum of 15 subjects with CD and a minimum of 10 subjects with impaired hand function.

2.1 Study objective(s)

2.1.1 Primary objective(s)

The primary objective of the study is to evaluate the ability of subjects in the Q2W and Q4W groups to safely and effectively self-inject certolizumab pegol (CZP) using the e-Device at Visit 2.

2.1.2 Secondary objective

The secondary objectives are to evaluate the ability of subjects in the Q2W and Q4W groups to safely and effectively self-inject CZP using the e-Device at Visit 1 and the structural integrity of used cassettes via visual examination.

2.1.3 Other objectives

The other objectives are to evaluate:

- The functional status of the e-Device following administration of the final study dose (ie, no visual signs of damage, device functions normally within training cassette)
- Subject experience of self-injection as assessed by the Pain Visual Analogue Scale (VAS) and Assessment of Self Injection (ASI)
- Subject preference for e-Device vs pre-filled syringe (PFS) using a self-administered Self-Injection Preference Questionnaire

2.1.4 Safety Objective

The safety objective is to evaluate the safety of CZP self-injection using the e-Device for CZP self-injection.

2.2 Study variables

2.2.1 Study outcome and variables

2.2.1.1 Primary outcome and variable

The primary outcome variable is the proportion (%) of subjects able to self-administer safe and effective injections using the e-Device at Visit 2. Safe and effective self-injection will be evaluated by the healthcare provider (HCP) and is defined as:

- Complete Dose Delivery: Subject self-injected the complete dose of CZP as confirmed by a visual inspection of the CZP-cassette(s) which shows the PFS container to be empty and

- No AEs related to use of the e-Device (ADEs) that would preclude continued use of the e-Device for self-injection

For subjects on the Q4W dosing regimen who will self-inject twice (2x200mg CZP) at each visit, each injection will be evaluated for safety and effectiveness using the above criteria. The primary endpoint of safe and effective self-injection for subjects on the Q4W dosing regimen will be met only if both self-injections are determined to be safe and effective.

2.2.1.2 Secondary outcome variables

The secondary variables are:

- The proportion (%) of subjects able to self-administer safe and effective injections using the e-Device at Visit 1. Safe and effective self-injection will be evaluated by the HCP and is defined as:
 - Complete Dose Delivery: Subject self-injected the complete dose of CZP as confirmed by a visual inspection of the CZP-cassette(s) which shows the PFS container to be empty and
 - No AEs related to use of the e-Device (ADEs) that would preclude continued use of the e-Device for self-injection

For subjects on the Q4W dosing regimen who will self-inject twice (2x200mg CZP) at each visit, each injection will be evaluated for safety and effectiveness using the above criteria. The primary endpoint of safe and effective self-injection for subjects on the Q4W dosing regimen will be met only if both injections are determined to be safe and effective.

- Percentage of used CZP-cassettes identified as having structural integrity issues based on visual examination (ie, clear evidence of damage/compromised structural integrity, not superficial cosmetic imperfections)

2.2.1.3 Other variables

The other outcome variables are:

- Injection site pain due to self-injection (using a VAS; 100mm) by visit at all visits after self-injection using e-Device

Subjects on the Q4W dosing regimen who will self-inject twice (2x200mg CZP) at each visit will complete the Pain VAS after the second injection at each of the 2 visits. For subjects on the Q4W dosing regimen, the Pain VAS will record the overall pain associated with both self-injections.

- Responses to the pre-injection Assessment of Self Injection (ASI) at Visit 1
- Responses to the post-injection ASI by visit at all visits after self-injection using the e-Device

Subjects on the Q4W dosing regimen who will self-inject twice (2x200mg CZP) at each visit will complete the post-injection ASI after the second injection at each of the 2 visits. For subjects on the Q4W dosing regimen, the post-injection ASI will collect the overall self-injection experience associated with both self-injections.

- Responses to the Self-Injection Preference Questionnaire

- In vitro functional evaluation of the e-Device following the final use per subject:
 - The percentage of e-Devices found to be functionally compromised (ie, visual signs of damage, device does not function normally with training cassette)

2.2.2 Safety variables

The safety variables are:

- Occurrence of AEs and ADEs
- Vital signs

2.3 Study design and conduct

In this Phase 3, open-label study of the e-Device, subjects diagnosed with RA, PsA, or AS (treated on a Q2W dosing schedule, Q2W group), or RA, PsA, AS, or CD (treated on a Q4W dosing schedule, Q4W group) will be recruited and evaluated. Subjects in the Q2W and Q4W group should currently be treated with commercial CZP and be performing self-administration using the PFS.

Hand function will be assessed at the screening visit by the Cochin Impaired Hand Function questionnaire. This study will recruit a minimum of 10 patients with impaired hand function. Impaired hand function will be measured using the Cochin scale and impaired hand function will be defined as patients who have a Cochin score ≥ 13.5 at baseline.

Participating subjects must be at least 18 years of age and on a stable CZP dosing regimen for at least 3 months before Visit 1.

Visit 1 should be scheduled to coincide with the individual treatment schedule for each subject. The study will consist of 2 site visits and a follow-up telephone call. Following an initial eligibility check at Visit 1, all eligible subjects will enter the Study Treatment Period at that same visit. Subjects will self-inject using the e-device immediately following training at Visit 1.

For subjects in the Q2W group, subjects will self-inject CZP 200mg using the e-Device (ie, 1x200mg injection). To meet the individual treatment schedule of the subjects, Visit 1 and Visit 2 should be consistent with their scheduled CZP dose (ie, 2 weeks between their last dose and Visit 1, and 2 weeks between Visit 1 and Visit 2).

For subjects in the Q4W group, subjects will self-inject CZP 400mg using the e-Device (ie, 2x200mg injections). To meet the individual treatment schedule of the subjects, Visit 1 and Visit 2 should be consistent with their scheduled CZP dose (ie, 4 weeks between their last dose and Visit 1, and 4 weeks between Visit 1 and Visit 2).

For both groups, a follow-up telephone call will be conducted 1 week after the final study drug administration as a safety follow-up call. Follow-up requirements for adverse events (Investigational Medicinal Product (IMP) and investigational device) and pregnancy are outlined in the protocol Sections 10.1.3, 10.2.3, and 10.3. Subjects who have a positive pregnancy test and who have self-administered at least 1 study dose of CZP who then discontinue CZP therapy will have a safety follow-up telephone call 70 days after the last study dose of CZP in addition to the 1-week Safety Follow-Up.

The study duration for each subject in the Q2W group on the Q2W dosing regimen is 3 weeks. The study duration for each subject in the Q4W group on the Q4W dosing regimen is 5 weeks.

Subjects will be required to perform a Safety Follow-Up by phone 1 week after their last study dose of CZP. Subjects who have a positive pregnancy test and who have self-administered at least 1 study dose of CZP who then discontinue CZP therapy will have a safety follow-up telephone call 70 days after the last study dose of CZP in addition to the 1-week Safety Follow-Up.

The end of study is defined as the date of the last telephone follow-up call for the last subject in the study.

2.3.1 Schedule of study assessment

Table 2-1: Schedule of study assessments for Q2W subjects

Assessments	Visit 1 (Week 0)		Visit 2 (Week 2) (±3 days)	Follow-Up ^a (Week 3) (±3 days)
	Screening	Study Treatment Period		
Written informed consent	X			
Demographic data	X			
Subject completes Cochin Impaired Hand Function questionnaire	X			
Verification of inclusion/exclusion criteria	X			
Withdrawal criteria				X
General medical/procedures history	X			
Physical examination ^b	X			
Vital signs ^c	X			X
Urine pregnancy test (βHCG) ^d	X			X
Contact IXRS	X			X
Recording of concomitant medication	X			X
Subject completes preinjection ASI		X		
Training with e-Device prior to self-administration		X		
Subject self-administers CZP using e-Device		X		X
HCP evaluates self-injection		X		X
Subject completes pain VAS (postinjection) ^e		X		X
Subject completes postinjection ASI ^f		X		X

Table 2–1: Schedule of study assessments for Q2W subjects

Assessments	Visit 1 (Week 0)		Visit 2 (Week 2) (±3 days)	Follow-Up ^a (Week 3) (±3 days)
	Screening	Study Treatment Period		
Assessment of structural integrity for CZP-cassette		X	X	
In vitro functional evaluation of e-Device			X	
Subject completes Self-Injection Preference Questionnaire			X	
Recording of AEs and ADEs		X	X	X

ADE=adverse device effect; AE=adverse event; AS=ankylosing spondylitis; ASI=Assessment of Self Injection; CZP=certolizumab pegol; HCP=healthcare provider; βHCG=beta human chorionic gonadotropin; IXRS=interactive response technology; Q2W=every 2 weeks; PsA=psoriatic arthritis; RA=rheumatoid arthritis; VAS=visual analog scale

Note: The visit window is ±3 days.

^a Subjects will be required to perform a Safety Follow-Up by phone 1 week after their last study dose of CZP. Subjects who are withdrawn from CZP treatment during the course of the study due to pregnancy will be required to perform a safety follow-up call 70 days following their final CZP administration in addition to the 1-week Safety Follow-Up.

^b Includes height and weight.

^c Includes blood pressure, pulse, body temperature, and respiratory rate.

^d For women of childbearing potential. A serum pregnancy test will be performed in the event of a positive urine result.

^e Immediately postinjection (within 15 minutes).

^f Within 30 minutes postinjection.

Table 2–2: Schedule of study assessments for Q4W subjects

Assessments	Visit 1 (Week 0)		Visit 2 (Week 4) (±3 days)	Follow-Up ^a (Week 5) (±3 days)
	Screening	Study Treatment Period		
Written informed consent	X			
Demographic data	X			
Subject completes Cochin Impaired Hand Function questionnaire	X			
Verification of inclusion/exclusion criteria	X			
Withdrawal criteria			X	

Table 2–2: Schedule of study assessments for Q4W subjects

Assessments	Visit 1 (Week 0)		Visit 2 (Week 4) (±3 days)	Follow-Up ^a (Week 5) (±3 days)
	Screening	Study Treatment Period		
General medical/procedures history	X			
Physical examination ^b	X			
Vital signs ^c	X		X	
Urine pregnancy test (βHCG) ^d	X		X	
Contact IXRS	X		X	
Recording of concomitant medication	X		X	
Subject completes preinjection ASI		X		
Training with e-Device prior to self-administration		X		
Subject self-administers CZP using e-Device		X	X	
HCP evaluates self-injection		X	X	
Subject completes pain VAS (postinjection) ^e		X	X	
Subject completes postinjection ASI ^f		X	X	
Assessment of structural integrity for CZP-cassette		X	X	
In vitro functional evaluation of e-Device			X	
Subject completes Self-Injection Preference Questionnaire			X	
Recording of AEs and ADEs	X		X	X

Table 2–2: Schedule of study assessments for Q4W subjects

Assessments	Visit 1 (Week 0)		Visit 2 (Week 4) (±3 days)	Follow-Up ^a (Week 5) (±3 days)
	Screening	Study Treatment Period		

ADE=adverse device effect; AE=adverse event; ASI=Assessment of Self Injection; CD=Crohn's disease; CZP=certolizumab pegol; HCP=healthcare practitioner; βHCG=beta human chorionic gonadotropin; IXRS=interactive response technology; Q4W=every 4 weeks; VAS=visual analog scale

Note: The visit window is ±3 days.

^a Subjects will be required to perform a Safety Follow-Up by phone 1 week after their last study dose of CZP. Subjects who are withdrawn from CZP treatment during the course of the study due to pregnancy will be required to perform a safety follow-up call 70 days following their final CZP administration in addition to the 1-week Safety Follow-Up.

^b Includes height and weight.

^c Includes blood pressure, pulse, body temperature, and respiratory rate.

^d For women of childbearing potential. A serum pregnancy test will be performed in the event of a positive urine result.

^e Immediately postinjection (within 15 minutes).

^f Within 30 minutes postinjection.

2.4 Determination of sample size

This study will not be powered with respect to any endpoint and sample size is based on practical considerations. The number of subjects and their diagnosed conditions are summarized below.

Approximately 80 subjects who are currently being treated with commercial CZP and are on a stable dosing regimen for at least 3 months will be screened in order to have at least 60 subjects use the e-Device at Visit 1. The 60 subjects using the e-Device at Visit 1 will be composed of a minimum of 15 subjects in each of the dosing groups (Q2W vs Q4W) with a minimum of 15 subjects with CD and a minimum of 10 subjects with impaired hand function. Impaired hand function will be measured using the Cochin scale (Poiraudieu et al, 2000; Duruöz et al, 1996) and impaired hand function will be defined as patients who have a Cochin score ≥13.5 at baseline.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

This is an estimation study design with no formal statistical hypothesis testing. All statistical analysis will be descriptive in nature. No inferential analyses are planned.

The study will estimate the true proportion and/or mean. Each endpoint will be summarized overall and by dosing group (Q2W or Q4W) and indication (RA, PsA, AS or CD).

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be carried out using SAS® Version 9.3 or higher.

Summary statistics for continuous variables will include the number of subjects with available measurement (n), mean, standard deviation (SD), median, minimum value, and maximum value.

For categorical variables, the number and proportion of subjects, along with the 90% confidence interval (CI) based on the Exact Binomial method, will be presented.

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.

Unless otherwise noted, all proportions will be displayed to 1 decimal place. No proportion will be displayed for zero counts, and no decimal will be presented when the proportion is 1.

No imputation of missing data will be performed.

All data recorded in the eCRF and questionnaires will be listed.

3.2 Analysis time points

3.2.1 Relative day

Relative day 1 is the date of first certolizumab pegol (CZP) administration via e-Device.

Relative day of date X = date X - Date of first CZP administration+1 if date X is on or after date of first CZP administration.

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

Relative days before first administration of CZP will have the prefix “-“.

Relative day after last dose will have the prefix “+”, and will be calculated from the date of last CZP administration (date X - date of last CZP administration+1). Relative day after last dose should typically only be calculated for the safety follow-up visit.

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

3.2.2 Mapping of assessments performed at Early Discontinuation Visit

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

In particular, vital signs and body weight are assessed at all Treatment Period visits, and so all assessments of these variables at EDVs corresponding to a scheduled visit will be mapped to the corresponding scheduled visit. If such assessment occurs at an unscheduled visit, it will be mapped to the next scheduled visit.

3.3 Definition of Baseline values

A Baseline value for a subject is defined as the latest non-missing measurement prior to self-injection at Visit 1.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary objective of the study. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the Data Cleaning Plan. To the extent feasible the rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

3.5 Analysis sets

3.5.1 Safety Set

The Safety Set (SS) will consist of all subjects of the study who have received at least 1 dose of CZP during the study (e-Device).

3.5.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the SS who received at least 1 dose of CZP using the e-Device in the study.

Since SS and FAS have the same definition in this study, the two sets will contain the same population. SS will be used for analyzing both safety variables and outcome variables in all presentations.

3.6 Treatment assignment and treatment groups

At Visit 1 and Visit 2, subjects on Q2W dosing regimen will self-inject CZP 200mg (1x200mg injection) using the e-Device. At Visit 1 and Visit 2, subjects on Q4W dosing regimen will self-inject CZP 400mg (2x200mg injections) using the e-Device. The actual dosing groups Q2W and Q4W will be used in presentation in the Tables, Figures and Listings (TFLs).

3.7 Center pooling strategy

Not applicable.

3.8 Coding dictionaries

Medical history and adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 19.0). Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL SEP/2015). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

Not applicable.

4 STATISTICAL/ANALYTICAL ISSUES

This is an estimation study design with no formal statistical hypothesis testing. The study will estimate the true population proportion and/or mean for the outcome variables. Each endpoint will be summarized overall and by dosing group (Q2W or Q4W) and indication.

Summary statistics for continuous variables will include:

- Number of available observations
- Mean, standard deviation, minimum, median, and maximum

For categorical variables, the number and proportion of subjects, along with the 90% confidence interval (CI) based on the Exact Binomial method, will be presented.

No imputation of missing data will be performed unless otherwise specified.

All data recorded in the eCRF and questionnaires will be listed by dosing group and indication within dosing group.

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

In the case of missing or partially missing dates, imputation rules for adverse events and medications shall be applied, so that concomitance (for medications) and treatment emergence (for adverse events) can be determined. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the eCRF.

4.2.1 Handling of prior and concomitant medications with missing data

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the eCRF.

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 date, 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 date is completely unknown, then use the date of first dose.

Imputation of Partial End 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 date is completely unknown, do not impute the stop date.

There will be no imputation of any other missing data.

4.2.2 Handling of adverse events with missing data

Any AEs with incomplete onset and outcome (end) dates will be handled according to the following rules for classification as treatment-emergent. Such imputations will only be performed for these classifications; in the listings all data will be shown as recorded on the eCRF.

- 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 onset, 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 onset, 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 onset, then use January 1 of the year of onset.
- If only the year is specified, and the year of first dose is the same as the year of onset, then use the date of first dose.
- If the AE onset date is completely unknown, then use the date of first dose.
- Imputations for missing end dates will not be performed for classification as treatment-emergent as this is not required.

Adverse events with missing severity or causality will be regarded as ‘severe’ and ‘related’ respectively for the tabulations. There will be no imputation of any other missing data. Any AE with additional missing data that prohibits classification for a given tabulation will be excluded from that tabulation.

In case of uncoded AEs, these AEs should be designated as “UNCODED” at all MedDRA levels, and such AEs will be included in summary tables and subject listings based on this classification.

4.3 Interim analyses and data monitoring

Not applicable.

4.4 Multicenter studies

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

4.5 Multiple comparisons/multiplicity

Not applicable.

4.6 Use of an efficacy subset of subjects

Not applicable.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

The following subgroups will be used for the analysis of primary outcome variable.

- Indication: RA, PsA, AS and CD.
- Dosing regimen: Q2W and Q4W.
- Impaired hand function: baseline Cochin score ≥ 13.5 .

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

A Subject disposition will include (at a minimum) summaries regarding screened and enrolled subjects, disposition by investigator, and reasons for discontinuation.

Summary tables of all subjects screened will be presented including reason for screen failures and disposition of subjects screened.

The number and percentage of subjects who completed the study, and who discontinued the study by discontinuation reasons will be summarized for subjects in the SS.

Study eligibility criteria will be listed and a separate listing of subjects who did not meet the eligibility criteria will be presented.

Subject disposition will be listed for all subjects screened. Listings of subject analysis sets, study discontinuation, and visit dates will be presented by subject including the relative day for the SS.

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types. Following different important protocol deviation types will be classified: inclusion criteria deviation, exclusion criteria deviation, withdrawal criteria deviation, prohibited concomitant medication use, AE/SAE Deviation, and procedural non-compliance. Summary tables of the number and percentage of subjects with an important protocol deviation will be provided for the SS.

A listing of all important protocol deviations identified at the data evaluation meeting will be presented by subject for all subjects in the SS, and will include deviation type and description.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Tables with descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) and listings will be given for the demographic variables age (at time of informed consent), gender, racial group, ethnicity, weight at Screening, height at Screening, body mass index (BMI). Age and BMI will be summarized as a continuous variable and as categorical

variables. Age will be combined based on the following categories: ≤ 18 , $19- < 65$, ≥ 65 years. BMI will be summarized based on the following categories: < 25 , $25- < 30$, ≥ 30 kg/m².

BMI in kg/m² is calculated based on the height (in m) and the weight (in kg) using the formula:

$$BMI = \frac{Weight}{Height^2}$$

Data collected in the CRF for female subject's childbearing potential and birth control will only be listed

6.2 Other Baseline characteristics

Hand function will be assessed at the screening visit by the Cochin Impaired Hand Function questionnaire. Cochin score will be calculated from the Cochin Impaired Hand Function questionnaire at Visit 1 Screening. There are 18 questions scored from 0 to 5. Total score will be calculated as the sum of all individual score. If there is any missing value in individual score, total score will not be calculated. Total score should range from 0 to 90. Results will be summarized as a continuous variable and as categorical variables. Cochin score will be based on the following categories: < 13.5 , ≥ 13.5 at Screening.

A listing will be provided for Cochin Impaired Hand Function questionnaire at Visit 1 Screening.

6.3 Medical history and concomitant diseases

Medical history and ongoing medical conditions will be summarized by MedDRA SOC and PT overall and by dosing group and indication. The denominator for the percentages will be the number of subjects in the SS.

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of study medication. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first CZP administration via e-Device. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For this study, that will include from the date of first self-administration of CZP via e-Device up to the SFU visit.

In the case of missing data, the classification of medications as prior and/or concomitant will be performed as described in [Section 4.2.2](#). Imputations of missing data will be performed before calculation of relative study days.

The number and percentage of subjects taking prior medications will be summarized overall and by dosing group and indication, and by anatomical therapeutic chemical (ATC) class, presenting Anatomical Main Group (ATC Level 1), and PT. The number and percentage of subjects taking concomitant medications will be summarized similarly. Tables for prior and concomitant medications will be presented for the SS.

Prior and concomitant medications will be listed by dosing group and indication within dosing group for the SS. Prior and concomitant procedures will be listed for reported term by dosing group and indication within dosing group.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance will be summarized based on the SS. Compliance will be examined in terms of completed injections, and will be calculated as:

$$\text{Percent compliance} = \frac{\text{number of completed injections}}{\text{number of expected injections}} \times 100$$

Where the number of injections expected is relative to the dosing group and when the subject finishes treatment. For example, for a subject on Q4W regimen prematurely discontinued from the study after Visit 1 due to AE, it is expected that this subject should complete 2 injections.

A summary of percent treatment compliance categorized as $\leq 50\%$, $> 50\%$ and $\leq 75\%$, and $> 75\%$ will be provided overall and by dosing group and indication.

8 OUTCOME ANALYSES

Outcome analysis will be performed on the SS overall and by dosing group and indication. All outcome variables will be listed.

All statistical analysis will be descriptive in nature. There is no formal statistical hypothesis testing or inferential analyses are planned. No p-values will be presented.

8.1 Statistical analysis of the primary outcome variable

The primary outcome variable is the proportion (%) of subjects able to self-administer safe and effective injections using the e-Device at Visit 2. Safe and effective self-injection will be evaluated by the healthcare provider (HCP) and is defined as:

- Complete Dose Delivery: Subject self-injected the complete dose of CZP as confirmed by a visual inspection of the CZP-cassette(s) which shows the PFS container to be empty and
- No AEs related to use of the e-Device (ADEs) that would preclude continued use of the e-Device for self-injection

For subjects with CD on the Q4W dosing regimen who will self-inject twice ($2 \times 200\text{mg CZP}$) at each visit, each injection will be evaluated for safety and effectiveness using the above criteria. The primary endpoint of safe and effective self-injection for subjects on the Q4W dosing regimen will be met only if both self-injections are determined to be safe and effective.

The number and proportion of subjects with safe and effective self-injections will be tabulated overall and by dosing group and indication. A subgroup analysis will be performed for subjects with impaired hand function. The 90% CIs for the proportion based on the Exact Binomial method will be reported as well.

8.1.1 Derivations of primary outcome variable

The primary endpoint of safe and effective self-injection will be met if both criteria are confirmed by the HCP and are recorded on the Study Medication Administration CRF form: (1) subject self-inject the complete dose of CZP as confirmed by visual inspection of the CZP-cassette(s) which shows the PFS container to be empty; (2) there are no AEs related to use of the e-Device (ADEs) that would preclude continued use of the e-Device for self-injection.

No imputation of missing data will be performed.

8.1.2 Analysis of the primary outcome variable

The number and proportion (%) of subjects who meet the primary endpoint of safe and effective self-injection at Visit 2 will be summarized overall and by dosing group and indication. Subjects who completed dose delivery, and subjects who has no AEs related to use of the e-Device will also be presented. The number of subjects who administered the self-injection at Visit 2 will be used as the denominator to calculate the proportion (%). The corresponding 90% CI based on Exact Binomial method will also be presented.

8.2 Statistical analysis of the secondary outcome variables

The secondary outcome variables will be summarized using descriptive statistics. All summary statistics will be presented overall and by dosing group and indication. A subgroup analysis will be performed for subjects with impaired hand function.

8.2.1 Proportion (%) of subject able to self-administer safe and effective injections at Visit 1

Safe and effective self-injection will be evaluated by the HCP at Visit 1 and is defined as:

- Complete Dose Delivery: Subject self-injected the complete dose of CZP as confirmed by a visual inspection of the CZP-cassette(s) which shows the PFS container to be empty and
- No AEs related to use of the e-Device (ADEs) that would preclude continued use of the e-Device for self-injection

For subjects with CD on the Q4W dosing regimen who will self-inject twice (2x200mg CZP) at each visit, each injection will be evaluated for safety and effectiveness using the above criteria. The endpoint of safe and effective self-injection for subjects on the Q4W dosing regimen will be met only if both self-injections are determined to be safe and effective at Visit 1.

The derivation of this secondary endpoint will follow the same algorithm as the derivation of the primary endpoint. No imputation of missing data will be performed.

The number and proportion (%) of subjects who meet the endpoint of safe and effective self-injection at Visit 1, as well as subjects who completed dose delivery, and subjects who has no AEs related to use of the e-Device will be summarized overall and by dosing group and indication. The number of subjects who administered the self-injection at Visit 1 will be used as the denominator to calculate the proportion (%). The corresponding 90% CI based on Exact Binomial method will also be presented.

8.2.2 Structural integrity of used CZP-cassettes

The trained site staff will inspect the used CZP-cassettes to determine if the used CZP-cassettes have structural integrity issues based on visual examination (ie, clear evidence of damage/compromised structural integrity, not superficial cosmetic imperfections). The assessment will be performed post each injection at Visit 1 and Visit 2.

The proportion (%) of cassettes with structural integrity issues will be summarized. The number of total cassettes will be used as the denominator to calculate the proportion (%). The corresponding 90% CI based on Exact Binomial method will also be presented.

8.3 Analysis of other outcome variables

The other outcome variables will be summarized using descriptive statistics. All other exploratory variables will be summarized overall and by dosing group and indication.

8.3.1 Injection site Pain (VAS)

A VAS will be used to assess overall injection pain due to self-injection at every visit during the Study Treatment Period. Subjects will be required to indicate their injection pain by placing a mark on a 100mm line from 0 (no pain) to 100 (worst possible pain). The VAS will be assessed immediately post injection (within 15 minutes). For subjects on the Q4W dosing regimen, the Pain VAS will record the overall pain associated with both self-injections.

Observed values of the injection site pain score at each visit will be summarized overall and by dosing group and indication using descriptive statistics.

8.3.2 Pre-injection ASI at Visit 1

The pre-injection ASI is composed of 6 items grouped into injections and self-confidence domains.

Domain score at Visit 1 will be summarized overall and by dosing group and indication using descriptive statistics. The domain score is calculated as the mean of the item scores included in the domain. Domain scores will be calculated only if at least half of the domain items are completed.

8.3.3 Post-injection ASI

The post-injection ASI is composed of 44 items grouped into 6 domains. The domains are feeling about injections, self-image, self-confidence, pain and skin reactions during and after injections, ease of use of the self-injection device, and satisfaction with self-injection.

Subjects on the Q4W dosing regimen who will self-inject twice (2×200mg CZP) at each visit will complete the post-injection ASI after the second injection at each of the 2 visits. For subjects on the Q4W dosing regimen, the post-injection ASI will collect the overall self-injection associated with both self-injections.

Domain scores at each visit will be summarized overall and by dosing group and indication using descriptive statistics. The domain score is calculated as the mean of the item scores included in the domain. Domain scores will be calculated only if at least half of the domain items are completed.

8.3.4 Self-injection preference questionnaire

The 9-item Self-Injection Preference Questionnaire was developed, based on patient input, to assess the self-injection experience and patient preference between the e-Device and PFS. The Self-Injection Preference Questionnaire will be completed by the subject at Visit 2 after the VAS. Subject response to each question will be summarized based on the following categories: ava®, your latest device, no preference. Responses will be summarized overall and by dosing group and indication using descriptive statistics.

8.3.5 Functional evaluation of the e-Device

The e-Device will also be evaluated for function integrity (ie, proper functioning) using a training cassette as specified in the in vitro e-Device functional testing directions.

The proportion (%) of e-devices found to be functionally compromised will be summarized. The corresponding 90% CI based on Exact Binomial method will also be presented.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

Not applicable.

9.2 Pharmacodynamics

Not applicable.

10 SAFETY ANALYSES

All safety summaries and listings will be performed using all subjects in the SS.

10.1 Extent of exposure

The duration of exposure (in days) for Q2W group will be calculated as:

$$\text{Duration of exposure} = \text{Date of last injection} - \text{Date of first injection} + 14$$

14 days refer to the treatment period of Q2W regimen.

The duration of exposure (in days) for Q4W group will be calculated as:

$$\text{Duration of exposure} = \text{Date of last injection} - \text{Date of first injection} + 28$$

28 days refer to the treatment period of Q4W regimen.

For subjects who die during the study, the duration of exposure (in days) will be calculated as:

$$\text{Duration of exposure} = \text{Date of death} - \text{Date of first injection} + 1$$

for both Q2W and Q4W.

The duration of exposure will be summarized overall and by dosing group and indication using descriptive statistics. A listing of data of first and last self-injection with e-Device will be provided.

10.2 Adverse events

10.2.1 Adverse event (IMP)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the

use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In this study, safety reporting requirements apply to all constituents of the IP (including CZP, the e-Device auto-injector, and the CZP-cassette) per 21 CFR 320. Adverse events related to use of the e-Device (ADEs) (including the CZP-cassette) will be summarized separately. Adverse events will be summarized by the frequency and percent of subjects having one or more of the events in question. Planned summaries include overall AEs, AEs by intensity, AEs by relationship to study drug, SAEs, AEs leading to withdrawal, AEs leading to death, ADEs, SADEs, and AEs of special interest.

Treatment-emergent AEs (TEAE) will be summarized overall and by dosing group and indication. Treatment-emergent AEs (TEAE) are those with onset date at or after the first self-injection with the e-Device up to 70 days after the last self-administration of study medication with the e-Device.

The incidence of TEAEs will be summarized by MedDRA SOC, high level term, and PT. Tables with incidences of classified TEAEs by maximum intensity, by relationship, and by subject number will be provided. Furthermore, the incidence of all TEAEs, serious TEAEs, TEAEs leading to study discontinuation and/or permanent withdrawal of study medication, TEAEs leading to death, and AE of special interest will be summarized. In addition, an overall summary table will be provided.

For each AE the following information will be listed for the SS: AE term (verbatim term), date of onset, pattern of event, whether or not the AE was classified as a SAE, as an AE of special interest, intensity, relationship to study medication, relationship to study device, action taken with study medication, other action taken, outcome, date of outcome, and whether the AE led to study drug discontinuation or to study discontinuation.

TEAEs with incidence of above reporting threshold of 5% of subjects will be summarized.

For all TEAEs the following variables will be calculated:

- Duration
- Time since first injection

10.2.2 Adverse device effect (investigation device)

An adverse device effect (ADE) is an AE related to the use of an investigational device.

The incidence of ADEs and serious ADEs will be summarized separately by MedDRA SOC, high level term, and PT. Each ADE will be listed for the SS.

10.2.3 AE of special interest

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

- Opportunistic infections
- Malignant and unspecified tumors
- Malignant tumors
- Serious cardiovascular events

- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Demyelinating-like disorders

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

- Serious infections
- Congestive heart failure
- Lupus and lupus-like illness
- Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

The following events are not officially considered to be AEs of interest but are nonetheless considered to be interesting enough to be summarized in stand-alone tables: 1) Hepatic events and 2) Hypersensitivity reactions and anaphylactic reactions.

Potential Hy's Law, defined as $\geq 3 \times \text{ULN}$ alanine aminotransferase or aspartate aminotransferase with coexisting $\geq 2 \times \text{ULN}$ total bilirubin in the absence of $\geq 2 \times \text{ULN}$ alkaline phosphatase, with no alternative explanation for the biochemical abnormality will also be summarized.

The approach for summarizing AEs of interest is detailed in the UCB AE of interest program specifications for Cimzia.

10.3 Vital signs

Vital signs will include systolic and diastolic blood pressure (BP), pulse, respiratory rate (RR), and body temperature. Vital signs will be measured at Visit 1 and Visit 2.

Vital signs will be summarized overall and by dosing group and indication using descriptive statistics and frequency tabulations. Summary statistics of vital sign values and change from baseline will be presented at each scheduled visit.

Temperature measurements will only be listed and not summarized in a table.

10.4 Physical examination

Physical examination abnormalities will be recorded in the eCRF only at Screening. Clinically relevant changes in subsequent physical examinations will be recorded as AEs. Physical examination findings at Screening will be listed.

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.

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RA0098 Statistical Analysis Plan

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